

Parkinson's Disease and Related Disorders

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DISTINGUISHING BETWEEN PARKINSON'S DISEASE AND PARKINSONISM

The syndrome of parkinsonism must be understood before understanding what is Parkinson's disease (PD). Parkinsonism is defined as any combination of six specific, independent motoric features: tremor at rest, bradykinesia, rigidity, loss of postural reflexes, flexed posture, and the freezing phenomenon (where the feet are transiently "glued" to the ground). Not all six of these cardinal features need be present, but at least two should be before the diagnosis of parkinsonism is made, with at least one of them being tremor at rest or bradykinesia. Parkinsonism is divided into four categories (Table 66-1). PD or primary parkinsonism will be the principal focus of this chapter; not only as it is the one that is most commonly encountered by the general clinician, it is also the one on which much research has been expended and the one we know the most about. The great majority of cases of primary parkinsonism are sporadic, but in the last decade, several gene mutations have been discovered to cause PD (Table 66-2). Whether genetic or idiopathic in etiology, the common denominator is that this group of primary parkinsonism is not caused by known insults to the brain (the main feature of secondary parkinsonism) and is not associated with other motoric neurological features (the main feature of Parkinson-plus syndromes). The uncovering of genetic causes of primary parkinsonism has shed light on probable pathogenic mechanisms that may be a factor in even the more common idiopathic cases of PD. It may even turn out that many of the idiopathic cases will be linked to gene mutations, discoveries yet to be made. Although the term "idiopathic PD" has been applied to primary parkinsonism, the fact that there are known genetic causes should encourage us to adopt the term "primary parkinsonism" rather than "idiopathic parkinsonism."

Three of the most helpful clues that one is likely dealing with a category of parkinsonism other than PD would be (1) a symmetrical onset of symptoms (PD often begins on one side of the body),

(2) a lack of a substantial clinical response to adequate levodopa therapy, and (3) the absence of rest tremor. The presence of any of these features does not necessarily exclude the diagnosis of PD, but the likelihood that the cause belongs to another category of parkinsonism is high. The clinical features suggesting a diagnosis favoring the other parkinsonian disorders and not PD are listed in Table 66-3. One common misdiagnosis is tremor owing to essential tremor, which can even be unilateral, although it more commonly is bilateral. Helpful in the diagnosis is that the tremor caused by PD is a rest tremor, whereas essential tremor is not present at rest, but appears with holding the arms in front of the body and increases in amplitude with intention activity of the arm, such as with handwriting or performing the finger-to-nose maneuver.

PD begins insidiously and gradually worsens. Symptoms, such as rest tremor, can be intermittent at the beginning, becoming present only in stressful situations. Patients with PD can live 20 or more years, depending on the age at onset; the mortality rate is approximately 1.5 times that of normal individuals of the same age. Death in PD is usually because of some concurrent unrelated illness or owing to the effects of decreased mobility, aspiration, or increased falling with subsequent physical injury. The Parkinson-plus syndromes typically progress at a faster rate and often cause death within 9 years. Thus, the diagnosis of PD is of prognostic importance, as well as of therapeutic significance, because it almost always responds to at least a moderate degree to levodopa therapy, whereas the Parkinson-plus disorders do not. While it may be difficult to distinguish between PD and Parkinson-plus syndromes in the early stages of the illness, with disease progression over time, the clinical distinctions of the Parkinson-plus disorders become more apparent with the development of other neurological findings, such as cerebellar ataxia, loss of downward ocular movements, and autonomic dysfunction (e.g., postural hypotension, loss of bladder control, and impotence).

There are no practical diagnostic laboratory tests for PD, and the diagnosis rests on the clinical features or by excluding some of the other causes of parkinsonism. The research tool of fluorodopa

TABLE 66-1**Classification of the Parkinsonian States**

Primary parkinsonism (Parkinson's disease)
Sporadic
Known genetic etiology (see Table 66-2)
Secondary parkinsonism (environmental etiology)
Drugs
Dopamine receptor blockers (most commonly antipsychotic medications)
Dopamine storage depletors (reserpine)
Postencephalitic
Toxins—Mn, CO, MPTP, cyanide
Vascular
Brain tumors
Head trauma
Normal pressure hydrocephalus
Parkinsonism-plus syndromes
Progressive supranuclear palsy (PSP)
Multiple system atrophy (MSA)
Cortical–basal ganglionic degeneration (CBGD)
Diffuse Lewy body disease (DLBD)
Parkinson–dementia–ALS complex of Guam
Progressive pallidal atrophy
Heredodegenerative disorders
Alzheimer's disease
Wilson disease
Huntington disease
Frontotemporal dementia on chromosome 17
X-linked dystonia-parkinsonism (in Filipino men; known as lubag)

positron emission tomography measures levodopa uptake into dopamine nerve terminals, and this shows a decline of approximately 5% per year of the striatal uptake. A similar result is seen using ligands for the dopamine transporter, either by positron emission tomography or by single photon emission computed tomography; these ligands also label the dopamine nerve terminals. All these neuroimaging techniques reveal decreased dopaminergic nerve terminals in the striatum in both PD and the Parkinson-plus syndromes, and do not distinguish between them. A substantial response to levodopa is most helpful in the differential diagnosis, indicating presynaptic dopamine deficiency with intact postsynaptic dopamine receptors, features typical for PD.

TABLE 66-3**Criteria to Exclude the Diagnosis of Parkinson's Disease in Favor of Another Cause of Parkinsonism**

	LIKELY DIAGNOSIS
History of:	
Encephalitis	Postencephalitic
Exposure to carbon monoxide, manganese, or other toxins	Toxin-induced
Recent exposure to neuroleptic medication	Drug-induced
Onset of parkinsonian symptoms following:	
Head trauma	Posttraumatic
Stroke	Vascular
Presence on examination of:	
Cerebellar ataxia	OPCA, MSA
Loss of downward ocular movements	PSP
Pronounced postural hypotension not because of concurrent medication	MSA
Pronounced unilateral rigidity with or without dystonia, apraxia, cortical sensory loss, alien limb	CBGD
Myoclonus	CBGD, MSA
Falling or freezing of gait early in the course of the disease	PSP
Autonomic dysfunction not because of medications	MSA
Excessive drooling of saliva	MSA
Early dementia or hallucinations from medications	DLBD
Dystonia induced with low-dose levodopa	MSA
Neuroimaging (MRI or CT scan) revealing:	
Lacunar infarcts	Vascular
Capacious cerebral ventricles	NPH
Cerebellar atrophy	OPCA, MSA
Atrophy of the midbrain or other parts of the brainstem	PSP, MSA
Effect of medication:	
Poor response to levodopa	PSP, MSA, CBGD, Vascular, NPH
No dyskinesias despite high-dose levodopa	Same as above

CBGD, cortical–basal ganglionic degeneration; DLBD, diffuse Lewy body disease, also called dementia with Lewy bodies; MSA, multiple system atrophy; NPH, normal pressure hydrocephalus; OPCA, olivo-ponto-cerebellar atrophy, which can be one form of MSA.

TABLE 66-2**Genetic Forms of Primary Parkinsonism**

NAME	GENE SYMBOL	PROTEIN	CHROMOSOME
Autosomal Dominant Transmission			
PARK1/PARK4	<i>SNCA</i>	α -synuclein	4q21.3
PARK5	<i>UCHL1</i>	Ubiquitin C-terminal hydrolase-L1	4p14
PARK8	<i>LRRK2</i>	Leucine rich repeat kinase 2	12p11.2–q13.1
	<i>GBA</i>	β -glucocerebrosidase	1q21
Dopa-responsive dystonia		GTP cyclohydrolase 1	14q22.1–q22.2
Autosomal Recessive Transmission			
PARK2	<i>PRKN</i>	Parkin (ubiquitin ligase)	6q25.2–q27
PARK6	<i>PINK1</i>	PTEN-induced kinase 1 (PINK1)	1p35–p36
PARK7	<i>DJ-1</i>	DJ-1	1p36
PARK9	<i>ATP13A2</i>	ATPase	1p32
Tyrosine hydroxylase deficiency			11p11.5

The development of dementia in a patient with parkinsonism remains a difficult differential diagnosis. If the patient's parkinsonian features did not respond to levodopa, the diagnosis is likely to be Alzheimer's disease, which can occasionally present with parkinsonism. If the presenting parkinsonism responded to levodopa, and the patient developed dementia over time, the diagnosis could be either PD dementia (PDD) or diffuse Lewy body disease (DLBD), also known as dementia with Lewy bodies. The nosologic distinction is less of substance and more of useful categorization. The term PDD is used if the symptoms of PD have been present for at least 1 year before dementia develops. The term DLBD is used if the symptoms of PD have been present less than 1 year before onset of dementia, or if dementia presents with the onset of parkinsonism. A major feature of PDD and DLBD is the presence of hallucinations. Without hallucinations, other types of dementias should be considered, including vascular disease, Alzheimer's disease, and frontotemporal dementia. DLBD is a condition where Lewy bodies are present in the cerebral cortex as well as in the brainstem nuclei. The hereditodegenerative disease, known as frontotemporal dementia, is an autosomal dominant disorder caused by mutations of the *tau* gene or the *progranulin* gene on chromosome 17; the full syndrome presents with dementia, loss of inhibition, parkinsonism, and sometimes muscle wasting. PDD is associated with aging and increased duration of PD. The prevalence of PDD is approximately 20%, but the likelihood of developing dementia eventually in a patient with PD is much greater, with the highest estimate around 78%.

Some adults may develop a more benign form of PD, in which the symptoms respond to very low-dose levodopa, and the disease does not worsen severely with time. This form is usually caused by the autosomal dominant disorder known as dopa-responsive dystonia, which typically begins in childhood as a dystonia. But when it starts in adult life, it can present with parkinsonism. There is no neuronal degeneration. The pathogenesis is because of a biochemical deficiency involving dopamine synthesis. The gene defect is for an enzyme, GTP cyclohydrolase 1, required to synthesize the cofactor for tyrosine hydroxylase activity, the crucial rate-limiting first step in the synthesis of dopamine and norepinephrine. Infantile parkinsonism is caused by the autosomal recessive deficiency of tyrosine hydroxylase, another cause of a biochemical dopamine-deficiency disorder. Young-onset PD—less than 40 years of age, but some use a cut-off of 50 years—usually worsens more slowly than those with older onset. But these young-onset patients are more likely to develop motor complications from levodopa therapy (see below).

PATHOLOGY OF PARKINSON'S DISEASE AND PARKINSON-PLUS SYNDROMES

Parkinson's disease and the Parkinson-plus syndromes have in common a degeneration of substantia nigra pars compacta dopaminergic neurons, with a resulting deficiency of striatal dopamine caused by loss of the nigrostriatal neurons. Accompanying this neuronal loss in the nigra is an increase in glial cells and a loss of the neuromelanin in the nigra, because neuromelanin is normally contained in the dopaminergic neurons. In PD, intracytoplasmic inclusions, called Lewy bodies, are usually present in many of the surviving neurons. It is recognized today that not all patients with PD have Lewy bodies, those with a homozygous mutation in the *parkin* (PARK2) gene,

mainly patients with young-onset PD, have nigral neuronal degeneration without Lewy bodies. Lewy bodies contain many proteins, including the fibrillar form of the protein α -synuclein. Immunostaining for α -synuclein is utilized today as the most sensitive histologic method to detect Lewy bodies. Recent research has shown that Lewy neurites (α -synuclein fibers in axons) first appear in the medulla and the olfactory bulb, and over time become present in a rostral manner up the brainstem, from medulla to pons to midbrain, and then into the thalamus and cerebral cortex. Thus, Lewy neurites (and Lewy bodies) do not start in the substantia nigra, which is located in the midbrain. There are no Lewy bodies in the Parkinson-plus syndromes.

A pathological feature of multiple system atrophy (MSA) is the presence of inclusions in oligodendroglia; these inclusions also contain α -synuclein. PSP and CBD contain tau filaments, and these two diseases share similar clinical features, especially in the late stages of these diseases. PSP shows neurofibrillary tangles in the substantia nigra and other nuclei, while CBD shows ballooned neurons, especially in areas of the cerebral cortex.

CAUSE AND PATHOGENESIS OF PARKINSON'S DISEASE AND PARKINSON-PLUS SYNDROMES

Other than known genetic causes of PD (Table 66-2), the etiology of these disorders remains unknown. Alterations in the *tau* gene have been implicated for PSP and CBD. Three of the identified genes causing PD (*PARK1*, *PARK2*, *PARK5*) point to an impairment of protein degradation with a build-up of toxic proteins that cannot be degraded via the ubiquitin–proteasomal pathway. This has led to the concept that perhaps most, if not all, cases of sporadic PD have an impairment of protein degradation. While *PARK1* represents mutations in the gene for α -synuclein, triplications and duplications of the chromosomal area for the *alpha-synuclein* gene (*PARK4*) also cause PD, indicating that accumulation of wild-type α -synuclein, and not just gene mutations of this protein are capable of causing neurodegeneration. A heterozygotic mutation in the gene for the lysosomal enzymes, β -glucocerebrosidase and a lysosomal ATPase (*PARK9*), indicates that faulty degradation of substrates can be an important pathogenic factor. One gene (*PARK6*) is involved with mitochondrial function, suggesting impaired energy metabolism can lead to PD. *PARK7* is a gene for a protein that fights oxidative stress; thus supporting the notion that increased oxidative stress can be a risk factor for PD.

The most common gene mutation causing PD is *PARK8*, especially the G2019S mutation; approximately 5% of familial cases and up to 2% of nonfamilial cases have this mutation. There is ethnic disproportion of specific mutations in the *LRRK2* gene. The G2019S mutation is highly prevalent in North African Arabs, Portuguese, Spanish, and Ashkenazi Jews. In the Chinese, the G2385R mutation is the most common. *LRRK2* is a complex protein with several functional domains, and mutations in any of them can lead to PD. It is not clear how such mutations cause the disease.

Because accumulated α -synuclein can cause porosity in the synaptic vesicle membrane, resulting in an outward leakage of stored dopamine, the increased cytosolic dopamine can auto-oxidize to form oxyradicals, such as dopamine quinone, to cause cell damage. Other pathogenic mechanisms being considered are (1) damage to the protein degradation properties of lysosomes leading to protein

accumulation and aggregation; (2) other effects from oxidative stress, such as the reaction of oxyradicals with nitric oxide to form the highly reactive peroxynitrite radical; (3) impaired mitochondria leading to both reduced ATP production and accumulation of electrons that aggravate oxidative stress, with the final outcome being apoptosis and cell death; and (4) inflammatory changes in the nigra producing cytokines that augment apoptosis. These concepts on pathogenesis are leading researchers to test agents that affect these potential mechanisms in an attempt to reduce the rate of neurodegeneration in PD.

EPIDEMIOLOGY AND CLINICAL FEATURES OF PARKINSON'S DISEASE

Although PD can develop at any age, it is most common in older adults, with a peak age at onset around 60 years. The likelihood of developing PD increases with age, with a lifetime risk of approximately 2%. A positive family history doubles the risk of developing PD to 4%. Twin studies indicate that PD with an onset before the age of 50 years is more likely to have a genetic relationship than for patients with an older age at onset.

The early symptoms and signs of PD are rest tremor, bradykinesia, and rigidity; these are related to progressive loss of nigrostriatal dopamine. These signs and symptoms result from dopamine deficiency and are usually correctable by levodopa and dopamine agonists. As PD progresses over time, non-dopamine-related symptoms develop, such as flexed posture, the freezing phenomenon, and loss of postural reflexes; these do not respond well to levodopa therapy. Moreover, increasing bradykinesia that is not responsive to levodopa can appear as the disease worsens. All these intractable symptoms lead to disability.

While the motor symptoms of PD dominate the clinical picture, and even define the parkinsonian syndrome, many patients with PD have other complaints that have been classified as *nonmotor*. These include bradyphrenia (slowness in mental function), decreased motivation and apathy, dementia (discussed above), fatigue, depression, anxiety, sleep disturbances (fragmented sleep and REM sleep behavior disorder), constipation, bladder and other autonomic disturbances (sexual, gastrointestinal), and sensory complaints. Sensory symptoms, including pain, numbness, tingling, and burning, in the affected limbs occur in approximately 40% of patients.

PRINCIPLES OF THERAPY

Parkinson-plus syndromes respond poorly to medications, so the emphasis here is on the treatment of PD. Certain principles serve as guidelines.

Neuroprotective Therapy

So far no drug or surgical approach has unequivocally been shown to slow the rate of progression of PD, but if any drug could be proven to delay the progression of the disease process, it should be incorporated early. Two drugs that have suggested evidence in the ability to slow the rate of clinical worsening are selegiline and rasagiline; both are irreversible MAO-B inhibitors with a propargylamine moiety in their chemical structure, which has been found to suppress apoptosis.

Encourage Exercise to Keep the Patient Mobile

An active exercise program encourages the patients to participate in their own care, allows muscle stretching and full range of joint mobility, and enhances a better mental attitude toward fighting the disease. One of the nonmotor symptoms of PD is the tendency to being passive with decreased motivation. Encouraging activity helps fight these symptoms. Studies in rodents have shown that those in enriched cages allowing exercise have slowed degeneration of dopamine neurons following toxin injections into those neurons, supposedly because of exercise leading to an increase in brain tropic factors.

Individualize Therapy

No two patients are identical; each presents with a unique set of symptoms, signs, response to medications, and a host of social, occupational, and emotional problems that need to be addressed. The treatment of PD, therefore, needs to be individualized. One takes into account the severity of the patient's symptoms, the degree of functional impairment, the expected benefits and risks of available therapeutic agents, and the age of the patient. Younger patients are more likely to develop motor fluctuations and dyskinesias from levodopa, while older patients are more likely to develop confusion, sleep-wake alterations, dementia, and psychosis.

Deep Brain Stimulation

Stereotaxic surgical implantation of electrodes with stimulation of the subthalamic nucleus has been shown to reduce motor symptoms of PD, especially bradykinesia, tremor, and rigidity. These are the same symptoms that respond to levodopa. The dopa-nonresponsive symptoms of PD also do not respond to deep brain stimulation (DBS). The best candidates for DBS are younger patients with a very good response to levodopa, but with the uneven response of motor fluctuations and dyskinesias. DBS can provide a smoothing out of the clinical response and allows a reduction of medications.

MEDICAL THERAPY OF PARKINSON'S DISEASE

Treatment of patients with PD can be divided into three major categories: physical (and mental health) therapy, medications, and surgery. Physical exercise is mentioned above, and should be implemented as soon as the diagnosis is made, but it is useful in all stages of disease. In the early stages of the disease, the joints should be fully stretched to compensate for the tendency of the patient to have a reduced range of motion. In advanced stages of PD, formal physical therapy is more valuable by keeping the joints from becoming frozen, and by providing guidance how best to remain independent in mobility, particularly with gait training. Medications are the mainstay of therapy, but DBS can be appropriate for selected patients as described above.

Dopamine replacement therapy is the major medical approach to treating PD, and a variety of dopaminergic agents are available (Table 66-4). The most powerful drug is levodopa, the immediate precursor of dopamine. Levodopa, an amino acid, can enter the brain, whereas dopamine is blocked by the blood-brain barrier. Levodopa is usually administered combined with a peripheral decarboxylase inhibitor

TABLE 66-4**Dopaminergic Agents**

Dopamine precursor: levodopa
Peripheral decarboxylase inhibitors: carbidopa, benserazide
Dopamine agonists: pramipexole, ropinirole, rotigotine, apomorphine
Catechol-O-methyltransferase inhibitors: tolcapone, entacapone
Dopamine releaser: amantadine
Peripheral dopamine receptor blocker: domperidone
MAO type B inhibitor: selegiline, Zydys selegiline, rasagiline

(carbidopa and benserazide) to prevent formation of dopamine in the peripheral tissues, thereby increasing levodopa's bioavailability and also markedly reducing gastrointestinal side effects. The brand name Sinemet is a combination of carbidopa and levodopa; the brand name Madopar is a combination of benserazide and levodopa. Such combination drugs are available in standard (i.e., immediate-release) and extended-release formulations. The former allows a more rapid and predictable "on," and the latter allows for a slightly longer plasma half-life, but with a slower and less predictable "on." The combination of the two release formulations can be administered in an attempt to smooth out and extend plasma levels of levodopa. One brand of carbidopa/levodopa is Parcopa that dissolves in the patient's mouth and enters the stomach via swallowing saliva. Its usefulness is for patients who have swallowing difficulties or who need to take a dose of carbidopa/levodopa quickly without delay in a search for liquid to swallow with a tablet. Although its pharmacokinetic profile is similar to a swallowed tablet of carbidopa/levodopa, many patients believe Parcopa works more quickly.

Although levodopa is the most effective drug to treat the symptoms of PD, approximately 60% of patients develop troublesome complications of disabling response fluctuations ("wearing-off" effect) and dyskinesias after 5 years of levodopa therapy, and younger patients (less than 60 years of age) are particularly prone to develop these problems even sooner. Thus, younger patients are often started with a dopamine agonist rather than levodopa (see below).

It should be pointed out that it is not safe to discontinue levodopa suddenly, such action can induce the neuroleptic-like malignant syndrome of fever, sweating, rigidity, and mental confusion and obtundation.

Besides being metabolized by aromatic amino acid decarboxylase (commonly known as dopa decarboxylase), levodopa is also metabolized by catechol-O-methyltransferase (COMT) to form 3-O-methyldopa. Two COMT inhibitors are available: entacapone and tolcapone. These agents extend the plasma half-life of levodopa with only slightly increasing its peak plasma concentration, and can thereby prolong the duration of action of each dose of levodopa. Their clinical indication is to help reduce motor fluctuations, i.e., increase "on" time and reduce "off" time. Because they enhance levodopa's efficacy, these agents can increase dyskinesias and the dosage of levodopa may need to be lowered.

Entacapone is very short acting, and each 200 mg tablet is taken simultaneously with levodopa; entacapone has been combined with carbidopa/levodopa into a single tablet, known as Stalevo. Tolcapone (100 and 200 mg tablets) is more potent and has a longer duration of action; it is taken three times daily. But it is encumbered with a greater likelihood to cause diarrhea and hepatic toxicity. Liver

function must be monitored and the drug stopped if abnormal liver chemistries are seen. Tolcapone is therefore given only if entacapone has been found to be ineffective in controlling motor fluctuations.

After levodopa, the next most powerful drugs in treating PD symptoms are the dopamine agonists. Several of these are available. The ergot compounds of pergolide, bromocriptine, and cabergoline have the potential to induce fibrosis (cardiac valvulopathy and retroperitoneal, pleuropulmonary, and pericardial fibrosis), so these agents are not recommended; indeed pergolide has been withdrawn from the U.S. market. Pramipexole and ropinirole appear to be equally effective at therapeutic levels. Dopamine agonists are more likely than levodopa to cause hallucinations, confusion, and psychosis, especially in the elderly. Thus, it is safer to utilize levodopa in patients older than 70 years. On the other hand, clinical trials have shown that dopamine agonists are less likely to produce dyskinesias and the wearing-off phenomenon than levodopa. But these trials also showed that levodopa provides greater symptomatic benefit than do dopamine agonists. Other problems more likely to occur with dopamine agonists than levodopa are sudden sleep attacks, including falling asleep at the wheel; daytime drowsiness; ankle edema; and impulse control problems such as hypersexuality and compulsive gambling, shopping, and eating.

The newest dopamine agonist is rotigotine, applied via a dermal patch to the upper torso or arms. Rotigotine penetrates the epidermis and dermis and enters the subcutaneous fat where it slowly enters the blood stream. The skin patch is applied once daily, usually after the morning shower, and is removed the next day before the shower; a new patch is applied to a different surface of the skin to reduce the chance of a rash, a common adverse effect. Absorption is steady over 24 hours, and three dose strengths (four in Europe) are available: 2, 4, and 6 mg/day (plus 8 mg/day in Europe). It is useful for those with swallowing difficulties and may help smooth out motor fluctuations and nocturnal akinesia, when the last prebedtime dose of levodopa does not last throughout the night. It is less potent than the other dopamine agonists, but its milder action may offer fewer adverse effects such as mental and behavioral side effects.

Apomorphine may be the most powerful dopamine agonist, but it needs to be injected subcutaneously (or taken sublingually in Europe). It is used to provide faster relief to overcome a deep "off" state.

Amantadine has several actions; it has antimuscarinic effects, but more importantly, it can activate release of dopamine from nerve terminals, block dopamine uptake into the nerve terminals, and block glutamate NMDA receptors. Its dopaminergic actions make it a useful drug to relieve symptoms in approximately two-thirds of patients, but it can induce livedo reticularis, ankle edema, visual hallucinations, and confusion. Its antiglutamatergic action is useful in reducing the severity of levodopa-induced dyskinesias, and in fact, is the only known effective antidyskinetic agent. The dose of amantadine for its anti-PD effect is usually 100 mg twice daily, but its antidyskinetic effect requires higher dosages, usually 300 to 400 mg/day. Unfortunately, the antidyskinetic effect tends to lessen over time. The elderly do not tolerate amantadine well because of mental adverse effects of confusion and hallucinations. Domperidone is a peripherally active dopamine receptor blocker and is useful in preventing gastrointestinal upset from levodopa and the dopamine agonists. It is not available in the United States, but is available in other countries. Monoamine oxidase type B (MAO-B) inhibitors

(selegiline, rasagiline, and Zydys selegiline) offer mildly effective symptomatic benefit and are without the hypertensive “cheese effect” seen with MAO-A inhibitors, and therefore can be used in the presence of levodopa therapy. Although there has been considerable debate about possible protective benefit with selegiline, recent studies evaluating its long-term use indicate that selegiline is associated with less freezing of gait and with a slower rate of clinical worsening compared to placebo-treated subjects. These benefits appear to be separate from its mild symptomatic dopaminergic effect, because all subjects were receiving the symptomatic benefit from concurrent levodopa therapy. Rasagiline is currently undergoing a large clinical trial to test its neuroprotective effect. Selegiline, but not rasagiline, is metabolized to L-amphetamine and methamphetamine. Zydys selegiline is a formulation of selegiline that dissolves under the tongue and is absorbed via the oral mucosa directly into the blood stream, thereby by-passing the gut and liver and not generating the amphetamines. All these drugs can reduce the severity of motor fluctuations with levodopa. They are more likely, however, to increase dyskinesias.

Nondopaminergic agents (Table 66-5) are useful to treat both motor and nonmotor symptoms in PD. Antimuscarinic drugs have been widely used since the 1950s, but these are much less effective than the dopaminergic agents, including amantadine. Because of sensitivity to memory impairment and hallucinations in the elderly population, antimuscarinics should be avoided in patients older than 70 years. They can reduce the severity of tremor. Antihistaminics have mild anticholinergic properties and can serve as alternatives to antimuscarinic drugs in the elderly population. Another alternative agent is the tricyclic amitriptyline, because it also has anticholinergic properties. Muscle relaxants can sometimes reduce muscle tightness and cramping, and might help overcome “off” dystonia and peak-dose dystonia that patients on levodopa therapy sometimes develop. Coenzyme Q10 is currently being tested in a controlled clinical trial to determine if it has protective effects.

Because depression is common in patients with PD, and often precedes the motor symptoms of PD, this mood disturbance needs to be vigorously addressed; the tricyclics and selective serotonin reuptake inhibitors are useful antidepressants. It is not certain if one

type of antidepressant class of compounds is superior to the other in treating the depression accompanying PD. If insomnia is a problem for the patient, using an antidepressant that is also a soporific can be doubly advantageous, such as amitriptyline given at bedtime.

The benzodiazepines can reduce anxiety and stress, and therefore are useful to decrease parkinsonian tremor that is exacerbated by stress. Diazepam is usually well tolerated and does not exacerbate parkinsonian symptoms. Lorazepam and alprazolam are other agents in this class of drugs.

Psychosis induced by levodopa and the dopamine agonists can usually be controlled by quetiapine and clozapine without worsening the parkinsonism. Other antipsychotic agents are more likely to worsen the parkinsonism, therefore, they should be avoided. Clozapine is more effective than quetiapine, but because clozapine treatment requires weekly white blood cell counts, quetiapine should be tried first. Both drugs are soporific and bedtime dosing is helpful to also overcome insomnia. Patients with PD often have no problem falling asleep, but they have frequent arousals (sleep fragmentation), and if they have trouble returning to sleep, a short-acting drug, such as zolpidem, taken when trying to fall back to sleep can be helpful. REM sleep behavior disorder (RBD) is common in patients with PD and MSA, and often precedes the appearance of these disorders. RBD is manifested by patients moving about while dreaming, i.e., acting out their dreams. Normally, dreaming in REM sleep is associated with muscle paralysis, and this is lost in RBD. The bed-partner is the one usually disturbed by the patient with RBD; the patients are unaware that they are thrashing and kicking in their dreams. Clonazepam taken at bedtime is an effective drug to overcome this problem. Excessive daytime sleepiness, due either to disrupted nighttime sleep or to drowsiness from medications (dopamine agonists and levodopa), can sometimes lessen with the administration of modafinil.

Cognitive decline and frank dementia can be helped to a limited and modest degree with centrally active cholinesterase inhibitors, donepezil and rivastigmine, which have undergone clinical trials in PDD. Orthostatic hypotension in PD can be owing to the disease (or to MSA) or to the medications, particularly levodopa, dopamine agonists, and antidepressants. Fludrocortisone and midodrine can overcome this symptom to some extent. Restless legs syndrome (RLS) is common in patients with PD, possibly induced by levodopa therapy, which is known to augment symptoms in patients with RLS (without concomitant PD) who had been placed on levodopa or dopamine agonists. Since RLS can cause nocturnal sleep disturbance, this symptom is worth enquiring about when patients complain of a restless sleep at night. The typical symptom of RLS is an uncomfortable feeling of discomfort in the legs (like crawling ants under the skin) late in the evening or night. Walking around relieves this symptom. Bedtime dose of a dopamine agonist or, if that fails, an opioid can provide effective relief.

TABLE 66-5

Nondopaminergic Agents

Parkinsonian motor symptoms:

- Antimuscarinics: trihexyphenidyl, bentrupine
- Antihistaminics: diphenhydramine, orphenadrine
- Antiglutamatergics (to reduce dyskinesia): amantadine
- Muscle relaxants: cyclobenzaprine, diazepam, baclofen
- Mitochondrial enhancer: coenzyme Q10

Nonmotor symptom control:

- Depression: selective serotonin reuptake inhibitors, tricyclics, ECT
- Anxiety: benzodiazepines—diazepam, lorazepam, alprazolam
- Psychosis (hallucinations, paranoia): clozapine, quetiapine
- Insomnia: quetiapine, zolpidem, benzodiazepine, mirtazapine
- REM sleep behavior disorder: clonazepam
- Excessive daytime sleepiness: modafinil
- Dementia: donepezil (Aricept), rivastigmine (Exelon)
- Orthostasis: fludrocortisone, midodrine (ProAmatine)
- Restless legs: dopamine agonists, opioids (e.g., propoxyphene, oxycodone)

MOTOR COMPLICATIONS OF LEVODOPA THERAPY

Many patients on levodopa therapy develop motor complications (Table 66-6). Response fluctuations usually begin as mild wearing-off, which can be defined as when an adequate dose of levodopa does not last at least 4 hours. Typically, in the first couple of years of treatment, there is a long-duration response so that the timing of doses of levodopa is not important. Over time, the long-duration

TABLE 66-6**Pattern of Development of Response Fluctuations, Dyskinesias, and Other Complications**

Dyskinesias (chorea and dystonia)
Peak-dose dyskinesias
Diphasic dyskinesias (beginning and end-of-dose dyskinesias)
Fluctuations
Wearing off
Delayed "ons"
Dose failures
Sudden, unpredictable "offs" (on-offs)
Early morning "off" dystonia
"Off" dystonia during day
Alertness
Drowsy from a dose of levodopa
Reverse sleep-wake cycle
Behavioral and cognitive
Vivid dreams
Benign hallucinations
Malignant hallucinations
Delusions
Paranoia
Confusion
Dementia

response becomes lost, and only a short-duration response occurs; patients then develop the wearing-off phenomenon. The "offs" tend to be mild at first, but over time become deeper with more severe parkinsonism; simultaneously, the duration of the "on" response becomes shorter. Eventually, some patients develop random, sudden "offs" in which the deep state of parkinsonism develops over minutes rather than tens of minutes, and they are less predictable in terms of timing with the dosings of levodopa. Many patients who develop response fluctuations also develop abnormal involuntary movements, i.e., dyskinesias.

Treatment of the "Wearing-off" Phenomenon

The wearing-off phenomenon, when mild, may be ameliorated slightly with the addition of selegiline (introduced as 5 mg daily, and increasing to 5 mg twice daily, as necessary) or rasagiline (0.5 mg once daily, and increasing to 1 mg once daily, as necessary). Both MAO-B inhibitors potentiate the action of levodopa, and their introduction can induce confusion and psychosis, particularly in the elderly. A lower dose of levodopa may be necessary. Sinemet CR (continuous release carbidopa/levodopa) can also be effective in patients with mild wearing-off, and one can gradually switch from standard carbidopa/levodopa to Sinemet CR, or use the combination of both immediate- and extended-release formulations. Because it takes more than an hour for a dose of continuous release medication to become effective, most patients will require simultaneous standard immediate release carbidopa/levodopa to obtain an adequate response. One can attempt to utilize standard carbidopa/levodopa alone, giving the doses closer together, but ultimately most patients will develop progressively shorter durations of effectiveness from these doses. So, patients could require as many as six or more doses per day, and then, eventually, dose failures owing to poor gastric emptying often develop.

Dopamine agonists, which have a longer biological half-life than levodopa, can also be used in combination with standard Sinemet or Sinemet CR. The addition of a dopamine agonist tends to make the "off" state less severe when used in combination with carbidopa/levodopa. The addition of a dopamine agonist, however, will likely increase dyskinesias; in this situation the dosage of levodopa would need to be reduced. Rotigotine (Neupro Dermal Patch) might be helpful to reduce mild wearing-off.

Catechol-O-methyltransferase inhibitors (COMTIs) have been found useful for treating wearing-off. Because of entacapone's short half-life, it is given with each dose of carbidopa/levodopa, and is equally effective as rasagiline in reducing the amount of daily "off" time. For those patients who have "offs" at a specific time of day, entacapone can be strategically given just with the dosage of carbidopa/levodopa that precedes this "off" period. Tolcapone, which can be tried if entacapone fails to provide adequate benefit, is taken three times daily with biweekly monitoring of the patient's liver enzymes. A typical dose of tolcapone is to start with 100 mg tid with an increase to 200 mg tid possible should the need arise. Because tolcapone can increase dyskinesia, using 50 mg tid on initiation of treatment for patients who already have dyskinesia is a more gentle approach. The COMTIs are effective immediately, which is a distinct advantage.

Behavioral or sensory "offs" can also occur as do motor "offs," often in the absence of any motor "off" which means a return of parkinsonism. Behavioral and sensory "offs" tend not to be easily recognized, because visibly the treating physician sees no motor changes. Behavioral/sensory "offs" can consist of pain, akathisia, depression, anxiety, dysphoria, or panic, and usually a mixture of more than one of these. Sensory "offs," like dystonic "offs" are extremely poorly tolerated. It is often the presence of one of these sensory and behavioral phenomena, more so than motoric parkinsonian or dystonic "offs," that drives the patient to take more and more levodopa, turning the patient into a "levodopa junkie."

Treatment of Levodopa-Induced Dyskinesias

Levodopa-induced dyskinesias are involuntary movements and occur in two major forms—chorea and dystonia. Choreic movements are irregular, purposeless, nonrhythmic, abrupt, rapid, unsustained movements that seem to flow from one body part to another. Dystonic movements are more sustained, twisting contractions. Many patients probably have a combination of chorea and dystonia. Dystonia is a more serious problem than chorea, because it is usually more disabling.

Peak dose dyskinesias occur when the plasma concentration of levodopa is at its peak, and the brain concentration of levodopa and dopamine is too high. Reducing the individual dosage can resolve this problem. But the patient may need to take more frequent doses at this lower amount, because reducing the amount of an individual dose also reduces the duration of benefit. More frequent dosing of levodopa tends to lead to delayed "ons" and dose failures eventually. A simple approach is to add amantadine, which suppresses the severity of dyskinesias, possibly because of its antiglutamatergic action. Start with a dose of 100 mg bid and increase up to 200 mg bid if necessary. Another approach is to add or substitute higher doses of a dopamine agonist while lowering the dose of carbidopa/levodopa. Dopamine agonists are less likely to cause dyskinesias, and therefore can usually be used in this situation quite safely. But adding the agonist while

maintaining the levodopa dosage will usually result in an increase of dyskinesias. If lowering the dose of levodopa results in more severe “off” states, then the agonists become more important. Sinemet CR is not helpful, because there is the danger of increased dyskinesias at the end of the day as the blood levels become sustained from frequent dosings of this extended release form of levodopa. Once dyskinesias appear with Sinemet CR, they last for considerable duration of time because of the slow decay in the plasma levels. In some patients, peak-dose chorea and dystonia occur at subtherapeutic doses of levodopa, and lowering the dose will render a patient even more parkinsonian. Such patients are candidates for deep brain stimulation (see below under Surgical Therapy).

Diphasic dyskinesias are dyskinesias that occur at the beginning and end of dose, not during the time of peak plasma and brain levels of levodopa. They tend to affect particularly the legs with a mixture of chorea and dystonia. Because the mechanism is unclear, treatment of diphasic dyskinesias is difficult. In this situation one should use a dopamine agonist as the major pharmacologic agent with supplementary levodopa.

“Off” *dystonia and painful “off” cramps* could be listed in both “dyskinesias” and “fluctuations,” because these dystonias occur when the patient is “off.” Dystonic spasms, therefore, can be either a sign of levodopa overdosage, as in peak-dose dyskinesias, or occur when the plasma level of levodopa is low, such as in early morning before the first dose of levodopa. “Off” dystonia can occur anytime when the patient is “off,” but most commonly in the early morning hours upon awakening and when the last prebedtime dose of levodopa has worn off. Usually, the dystonia manifests as painful foot and toe cramps, which are relieved when the next dose of levodopa begins to take effect. Preventing “offs” is the best way to control these painful dystonias. An effective treatment is to use a dopamine agonist as the major pharmacologic agent with supplementary levodopa. Here the rotigotine dermal patch can be particularly useful, by keeping a steady pharmacokinetic level of active drug throughout the day and night. Baclofen has also been reported to benefit some patients. Bedtime Sinemet CR may be useful to prevent early-morning dystonia, but some patients need to set the alarm early to take a dose of standard carbidopa/levodopa in the middle of the night and then fall back to sleep and awaken at their usual time.

TREATMENT OF NONMOTOR FEATURES

In addition to PD having motor features, a number of nonmotor problems can also occur as complications from dopaminergic therapy. Mental changes of psychosis, confusion, agitation, hallucinations, paranoid delusions, and excessive sleeping are probably related to activation of dopamine receptors in nonstriatal regions, particularly the cortical and limbic structures. Elderly patients and patients with concomitant dementia are extremely sensitive to small doses of levodopa. But all patients with PD, regardless of age, can develop psychosis if they take excess amounts of levodopa as a means to overcome “off” periods.

If hallucinations are mild and not frightening, treatment can begin with the addition of quetiapine, starting with 25 mg at bedtime. The dose should be increased steadily until the hallucinations are brought under control. If quetiapine is ineffective or if the hallucinations are frightening, clozapine needs to be initiated instead of quetiapine, because clozapine is more effective than quetiapine. The

reason clozapine is not the first drug of choice in dopaminergic-induced hallucinations is because clozapine causes agranulocytosis in approximately 1% to 2% of patients. Patients must have their blood counts monitored weekly for this potential complication, and then discontinue the drug if leukopenia develops. Both quetiapine and clozapine often cause drowsiness, so bedtime dosing is recommended. Quetiapine can cause falling, and clozapine, seizures with high doses. The dosing regimen for clozapine is similar to that for quetiapine. Quetiapine and clozapine are labeled as “atypical antipsychotics,” because they usually do not induce or worsen parkinsonism, and therefore can be used in patients with PD. Of the other antipsychotic drugs, olanzapine ranks next as being “atypical,” but this drug will worsen PD, most atypical are quetiapine and clozapine. All the other antipsychotics, regardless if they had in the past been considered to be “atypical,” actually are not, for they all worsen PD.

If the psychosis is severe or if the patient is in an acute delirious state, hospitalization is necessary, with immediate initiation of high doses of clozapine, and some reduction in anti-PD medication. These medications could even be withdrawn temporarily to overcome the psychosis, but this should be done stepwise over a 3-day period to avoid the neuroleptic-malignant-like syndrome that could occur with sudden withdrawal of levodopa.

If hallucinations are mild and the patient can be treated as an outpatient, and the patient does not respond well or tolerate quetiapine and clozapine, then the physician needs to reduce one or more anti-PD medication. All antiparkinson drugs have the potential to induce psychosis, so the less efficacious drugs should be withdrawn first. Accordingly, COMT inhibitors, MAO-B inhibitors, amantadine, anticholinergics, and dopamine agonists should be withdrawn in that order, reserving levodopa as the most effective agent.

An altered sleep–wake cycle of drowsiness during the daytime, particularly after a dose of levodopa, and insomnia at night are fairly common in the elderly and often accompany cognitive decline. If a patient becomes drowsy after each dose of medication, reducing the dose may correct this problem. If the patient is generally drowsy during the daytime and remains awake at night, this makes it difficult for the care provider. It is important to get the patient onto a sleep–wake schedule that fits with the rest of the household. Efforts must be made to stimulate the patient physically and mentally during the daytime and force him/her to remain awake, otherwise he/she would not be able to sleep at night. At night, the patient should then be drowsy enough to be able to sleep. If this fails, it may be necessary to use stimulants in the morning and sedatives at night in order to reverse the altered state. This should be done in addition to prodding the patient to remain awake during the day. Modafinil can sometimes be helpful to overcome daytime drowsiness, and one or two doses in the morning and early afternoon can be employed. Drugs such as methylphenidate and amphetamine are usually also well tolerated by patients with PD, and can be considered if modafinil fails. A 10-mg dose of either of these two drugs, repeated once if necessary, may be helpful. To encourage sleep at night, a hypnotic may be necessary in addition to using daytime stimulants. It should be noted that strong sedatives, such as barbiturates, are poorly tolerated by patients with PD. Milder hypnotics, such as benzodiazepines and zolpidem, are usually taken without difficulty. Taking advantage of the soporific effects of quetiapine, clozapine, mirtazapine, and amitriptyline is a good strategy if a patient can also benefit from their other actions of antipsychotic or antidepressant.

Orthostatic hypotension can be caused by levodopa, dopamine agonists, and other drugs taken by the patient, such as tricyclic antidepressants. These other drugs should be discontinued. If orthostatic hypotension remains, it can sometimes be managed by using support stockings, NaCl, midodrine (ProAamate), and fludrocortisone (Florinef), but often the dose of levodopa needs to be reduced.

Constipation is common in PD. It may be further aggravated by anticholinergics. Besides changing dietary habits by increasing intake of more fiber and dried fruits, polypropylene glycol (Mira-Lax) can be effective. For those who have bloating because of suppression of peristalsis when they are “off”, keeping them “on” with levodopa is beneficial.

Depression is a common nonmotor symptom in PD, probably related to the reduction of all brain monoamines in this disease. Depression must be treated, not only for its own sake, but because its presence interferes with a good response to antiparkinson drugs. It often responds to selective serotonin reuptake inhibitors, such as fluoxetine, sertraline, and paroxetine, and those agents like nefazodone and venlafaxine that inhibit both serotonin and norepinephrine. It is not clear if any antidepressant is superior to any other, including the tricyclic antidepressants, such as amitriptyline, nortriptyline, and protriptyline. Because of its anticholinergic and soporific effects, amitriptyline can be useful for these properties as well as for its antidepressant effect. Protriptyline, on the other hand, has no anticholinergic effect and can be useful when this property is not needed. Electroconvulsive therapy can be effective in patients with severe, intractable depression, and it can sometimes transiently improve the motor symptoms of PD as well.

Impulse control problems have emerged in the last few years as a complication of dopamine agonists that had not been recognized previously. These consist of behavioral changes such as compulsive gambling, shopping, and eating, and hypersexual desire. Although infrequent, these can be serious problems. So far, the only remedy has been to reduce the dose of the dopamine agonists or stop them altogether.

SURGICAL THERAPY

Surgery for PD is becoming increasingly available as deep brain stimulation has evolved along with a better understanding of basal ganglia physiology. Stereotaxic DBS has replaced the older technique of lesioning in the brain, because the latter is more risky for inducing permanent neurological deficits. With DBS, the parameters of stimulation, such as voltage and frequency, can be adjusted, and the electrodes could be removed if required. However, DBS is more costly, and frequent adjustments of the stimulators are usually needed. The location of the stereotaxic target is a major factor that needs to be individualized for each patient. The subthalamic nucleus (STN) is the favored target, because this reduces bradykinesia and

tremor, allowing for a reduction of levodopa dosage, thus reducing the severity of dyskinesias as well. The internal segment of the globus pallidus is a more satisfactory target for controlling choreic and dystonic dyskinesias, which in turn would allow a higher dose of levodopa to be used to control the major symptoms of PD. The thalamus, particularly the ventral intermediate nucleus, is the target most successful for controlling tremor, but this target does not eliminate bradykinesia as well as the STN does, so the thalamus is not a preferred choice today. Surgical procedures for patients with PD are best performed at specialty centers with an experienced team of a neurosurgeon, neurophysiologist to monitor the target during the operative procedure, and neurologist to program the stimulators. The patient needs close follow-up to adjust the stimulator settings to their optimum. Patients with cognitive decline should not have DBS, because cognition can be further impaired. Also, intractable symptoms of freezing of gait, loss of postural reflexes, and falling are not benefited. The major benefits of STN stimulation are those symptoms that respond to levodopa. Adverse effects include surgical complications, mechanical problems with the stimulator and leads to the electrodes, infections attacking any of the inserted hardware, and neurologic and behavioral changes. The latter include troubles with speech, dystonic postures, depression, suicide attempts, and cognitive decline. The best candidates are younger patients who can tolerate the penetration of the brain and who have uncontrollable motor fluctuations and dyskinesias.

FURTHER READING

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