

2015 Update on Parkinson disease

ABSTRACT

Parkinson disease is still diagnosed by clinical signs, and its most effective treatment is still levodopa. However, an improved understanding of the disease is leading to new diagnostic tools and treatments.

KEY POINTS

Parkinson disease is diagnosed by clinical signs with the mnemonic TRAP: **T**remor at rest, **R**igidity, **A**kinesia or bradykinesia, and **P**ostural/gait instability.

A dopamine transporter functional scan can distinguish neurodegenerative parkinsonian disorders from nonneurodegenerative etiologies such as drug-induced parkinsonism and vascular parkinsonism, and from mimics such as psychogenic parkinsonism and essential tremor.

Coffee consumption and exercise may benefit patients with Parkinson disease.

Carbidopa-levodopa combination therapy is still the most effective treatment, but most patients develop dyskinesia after 5 to 10 years of treatment.

Dyskinesias can be managed by adjusting or changing medications, switching to the new levodopa infusion pump system, or with deep-brain-stimulation surgery.

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THIS has been a boom year for Parkinson disease, with the US Food and Drug Administration (FDA) approving two new therapies, and with others in the pipeline.

This article details clinical signs of Parkinson disease, discusses functional imaging, provides an update on current thinking on disease pathogenesis, and gives an overview of managing parkinsonian symptoms and dyskinesias.

■ DIAGNOSIS REMAINS CLINICAL

Although a better understanding of Parkinson disease has been gained in recent years, with the recognition of several premotor features and potential biomarkers, its diagnosis is still primarily based on clinical motor findings. The four cardinal motor features have the mnemonic TRAP:

- **Tremor at rest** can be subtle, involving just the thumb, best observed when the patient is sitting with the hand resting on the lap; or it can be obvious, involving the entire hand, arm, feet, lips, and chin.
- **Rigidity** can be felt rather than seen, by slowly passively rotating the patient's wrist or elbow and feeling resistance. The right and left sides often differ.
- **Akinesia or bradykinesia** (slowness or lack of movement) can be observed by having the patient walk down a hallway. One may observe reduced arm swing and hesitation in initiating movement.
- **Postural instability** usually develops later rather than sooner in the disease progression. The patient may need to hold onto someone to maintain balance when getting up or walking.

At least two features must be present to make the diagnosis of parkinsonism. One feature must be tremor or rigidity.

Although the criteria for parkinsonism ap-

**Dopamine transporter SPECT:
A tool for narrowing the diagnosis of parkinsonian symptoms**

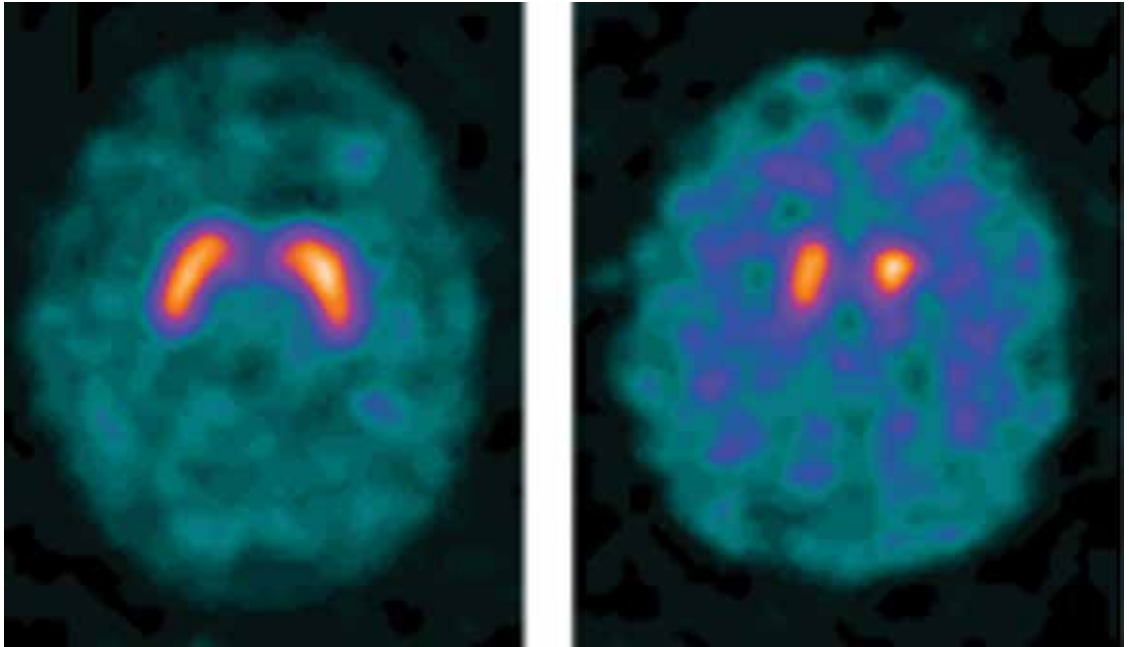


FIGURE 1. Dopamine transporter single-photon emission computed tomography (SPECT) can be used to narrow the diagnosis in patients with parkinsonian symptoms. **Left**, a normal result, which is characteristic in those whose symptoms are due to essential tremor, psychogenic causes, drugs, stroke (unless the basal ganglia are involved), normal-pressure hydrocephalus, or arthritis. **Right**, an abnormal result can be seen in idiopathic Parkinson disease, progressive supranuclear palsy, multiple system atrophy, corticobasal degeneration, or Lewy body disease.

The TRAP features of Parkinson disease:

- Tremor
- Rigidity
- Akinesia
- Postural instability

pear simple, the diagnosis of Parkinson disease is not always clear-cut. For example, shaking can be secondary to a dopamine receptor-blocking medication, to anxiety, or to essential tremor; rigidity and slowness may be due to arthritis; and postural instability can result from a neuropathy. Moreover, other neurodegenerative parkinsonian disorders may respond to levodopa (at least initially) and may present with levodopa-induced dyskinesias. Robust response to levodopa and the occurrence of dyskinesias are two additional features that strongly suggest the diagnosis of Parkinson disease.

Supporting parkinsonian features include stooped posture, masked facies, micrographia (small handwriting), drooling, speech changes (eg, hypophonia or soft speech, stuttering, slurring, monotonic speech), and a shuffling, festinating gait (quick short steps as if falling forward).

■ PARKINSON MIMICS

Parkinsonism is a broader term than *Parkinson disease* or *idiopathic Parkinson disease*. It is characterized by akinetic rigidity and impaired motor activity that leads to reduced function and falls; behavioral changes also may occur.

In the United States, Parkinson disease is the most common cause of parkinsonism. Other nonneurodegenerative causes are drug-induced parkinsonism (due to dopamine receptor antagonists such as antipsychotic or antiemetic drugs), stroke (in the basal ganglia or frontal lobe), and normal-pressure hydrocephalus (causing lower-body parkinsonism). Mimics of parkinsonism include essential tremor and psychogenic parkinsonism.

Parkinsonism can also be caused by Parkinson-plus disorders, ie, neurodegenerative conditions characterized by parkinsonism along with additional signs and symptoms, as

listed below. Parkinson-plus disorders include progressive supranuclear palsy, multiple system atrophy, corticobasal degeneration, and Lewy body disease.

Clinical features that suggest a diagnosis other than Parkinson disease include¹:

- Poor response to adequate dosages of levodopa
- Early onset of postural instability and falls
- Axial rigidity (eg, stiff neck) more than appendicular rigidity
- Early dementia
- Supranuclear gaze palsy
- Unusual movements besides tremor, eg, limb dystonia, myoclonus, limb levitation or alien limb syndrome
- Profound autonomic dysfunction
- Psychotic symptoms before taking levodopa or dopaminergic medication.

The precise diagnosis of Parkinson-plus disorders is not critical, as the treatment is generally the same for all of them: ie, levodopa (if it shows some efficacy and is well tolerated), with additional symptomatic treatment for features such as depression, cognitive impairment, and autonomic dysfunction, and supportive therapy including physical, occupational, speech, and swallowing therapy.

■ IMAGING MAY ASSIST IN THE DIAGNOSIS

Dopamine transporter single-photon emission computed tomography (SPECT) is a functional imaging technique that supposedly reflects dopamine uptake by surviving presynaptic dopaminergic neurons in the striate bodies of the basal ganglia. Normal uptake shows distinct cashew-shaped enhancement bilaterally. In Parkinson disease, the enhanced areas are smaller and asymmetric, first with diminution of the tail (representing the putamen), then later involving the head (representing the caudate) along with the other striate bodies (Figure 1).

Dopamine transporter SPECT does not distinguish one neurodegenerative parkinsonian disorder from another. Therefore, it should not be used to distinguish Parkinson disease from other Parkinson-plus syndromes. But it does distinguish neurodegenerative parkinsonian disorders from nonneurodegenerative conditions and mimics, which have a nor-

TABLE 1

Differential diagnosis of dopamine transporter SPECT

Normal result

- Psychogenic parkinsonism
- Drug-induced
- Stroke (unless the basal ganglia are involved)
- Normal-pressure hydrocephalus
- Arthritis

Abnormal result

- Idiopathic Parkinson disease
- Progressive supranuclear palsy
- Multiple system atrophy
- Corticobasal degeneration
- Lewy body disease

SPECT = single-photon emission computed tomography

mal result on dopamine transporter SPECT (Table 1).

■ SLOWING DISEASE PROGRESSION

Current treatments for Parkinson disease can significantly improve symptoms but, unfortunately, do not cure the disease or slow its progression. Testing whether agents modify the disease course is particularly difficult with Parkinson disease, because it affects individuals differently, has a wide spectrum of symptoms, has a long time course, and lacks definitive markers to monitor progression. Some agents have shown promise:

Caffeine. People who drink coffee are less likely to develop Parkinson disease, with the risk declining with the number of cups per day.² For those who have the disease, drinking coffee is associated with reduced symptoms.

Exercise improves Parkinson disease and may prevent it, and some studies suggest that it can delay its progression.³ Exercise has been shown in an animal model to reduce the vulnerability of dopamine neurons to the toxic agent 6-hydroxydopamine.⁴ Functional magnetic resonance imaging studies have shown blood flow patterns before and after exercise

The diagnosis is not always clear-cut

that are similar to those seen in patients with and without Parkinson medication.³

Rasagiline, a monoamine oxidase B (MAO-B) inhibitor used for symptomatic treatment of Parkinson disease, had conflicting results in a neuroprotective clinical trial. Patients who received rasagiline 1 mg daily—but not those who received 2 mg daily—at the beginning of the trial had better Parkinson motor scores compared with patients who received rasagiline 9 months later.⁵

Inosine is a urate precursor that elevates urate levels in serum and the central nervous system. For unknown reasons, patients with Parkinson disease tend to have a low uric acid level, and higher levels are associated with milder disease. It is hoped that raising the uric acid level to a “pre-gout level” may slow the progression of Parkinson disease.

Isradipine, a calcium channel blocker, was found in an epidemiologic study of elderly patients to be associated with reduced likelihood of developing Parkinson disease.⁶ The drug is now undergoing clinical trials.

Smoking. Although cigarette smokers have long been recognized as having a very low risk of developing Parkinson disease, smoking is not recommended.

Agents found ineffective. Agents that have been tested and found ineffective in modifying the course of Parkinson disease include vitamin E, coenzyme Q10, riluzole, GPI-1485, pramipexole, cogane, CEP-1347, TCH-346, and creatine.

■ NOT JUST DOPAMINE—OR TREMORS

Dopamine deficiency is central to the current understanding of the pathogenesis of Parkinson disease and the focus of treatment efforts, but if dopamine deficiency were the only problem, replacing it should completely ameliorate all parkinsonian features. Other neurotransmitters also play roles: norepinephrine is implicated in orthostatic symptoms and apathy, acetylcholine in cognitive behaviors, glutamate in dyskinesias, and serotonin in depression, anxiety, and sleep abnormalities.

The most recognized area of involvement in the brain has traditionally been the substantia nigra in the midbrain. However, current thinking is that the disease starts lower in the caudal area of the brainstem (along with the

olfactory tubercle), moves through the pons to the midbrain, then spreads across the cerebrum with extensive neocortical involvement.

Early premotor indicators are now recognized to occur 15 to 20 years before a tremor appears. The first signs are often hyposmia (diminished sense of smell, reflecting involvement of the olfactory tubercle) and constipation (reflecting involvement of the medulla and the vagus nucleus). With pons involvement, the patient can develop rapid eye movement sleep behavior disorder, depression, or anxiety. Only then does the disease spread to the midbrain and cause resting tremor, rigidity, and bradykinesia.⁷

Identifying the preclinical stages and starting disease-modifying treatments before the onset of motor symptoms may one day prove important, but at this point, the premotor symptoms (anosmia, constipation, depression) are too nonspecific to be useful, and such treatments have not yet been identified.

■ TREATMENT: LEVODOPA STILL PRIMARY

When to start drug treatment depends primarily on how much the symptoms bother the patient. Regardless of the clinician’s (or patient’s) belief in the benefits of delaying symptomatic treatment, it is universally considered necessary to start medication when gait problems develop because of the danger of a fall and resulting disability.

Carbidopa-levodopa combination therapy remains the most effective treatment; if it is not effective, another diagnosis may need to be considered. Carbidopa-levodopa improves tremor, rigidity, and bradykinesia, particularly in the early stages of Parkinson disease. It is well tolerated, has rapid onset, reduces the risk of death, and is the least expensive of the medications for Parkinson disease.

Immediate-release and continued-release formulations are available, as well as one that dissolves rapidly on the tongue and can be taken without water. An oral extended-release carbidopa-levodopa formulation (Rytary) was approved by the FDA in January 2015. Tablets are filled with drug-containing microbeads that dissolve at different rates to achieve therapeutic levodopa levels as quickly as the immediate-release formulation and maintain them for an extended time.⁸

The precise diagnosis of Parkinson-plus syndromes is not critical

The development of dyskinesias is the major psychological drawback of levodopa, occurring in 80% of patients after 5 to 10 years of treatment. Although many patients fear this side effect, most patients who develop it find it preferable to the rigidity and bradykinesia of Parkinson disease. In most cases, bothersome dyskinesias can be controlled by adjusting medications.^{9,10}

Dopamine agonists include pramipexole, ropinirole, and rotigotine. They are available in generic form as three-times-daily dosing; once-daily dosing is also available, but not as a generic formulation. Dopamine agonists have the advantage of potentially improving depression and delaying the onset of dyskinesias.

However, dopamine agonists have a number of disadvantages compared with levodopa: they have a longer titration period, are less effective, and are less well tolerated, especially in the elderly. Side effects occur more frequently than with levodopa and include general and peripheral edema, hallucinations, nausea, lightheadedness, and sleepiness.^{11,12} These drugs are also associated with “sleep attacks” (sudden falling asleep while active, such as while driving or eating) and with compulsive and impulsive behaviors such as hypersexuality, buying, binge eating, and gambling. Although these behaviors occur in fewer than 10% of patients, they can be devastating, leading to marital, financial, and legal problems. A bothersome clinical state termed *dopamine agonist withdrawal syndrome* is characterized by anxiety, depression, jitteriness, and palpitations when dopamine agonists are tapered or discontinued because of a side effect.¹³

MAO-B inhibitors delay the breakdown of dopamine, allowing it to “stay” in the brain for a longer period of time. Rasagiline for early monotherapy has the advantages of once-daily dosing, no titration, and excellent tolerability, even in the elderly. Potential drug interactions should be considered when using this drug. Early warnings about interactions with tyramine-rich foods were lifted after trials showed that this was not a problem.¹⁴

Amantadine is an *N*-methyl-D-aspartate (NMDA) receptor antagonist often used in early Parkinson disease and for treatment of dyskinesias and fatigue. It is the only drug that is intrinsically antidyskinetic and also

improves Parkinson symptoms.¹⁵ Side effects include leg swelling, livedo reticularis, and neuropsychiatric and anticholinergic effects.

Anticholinergic agents (eg, trihexyphenidyl) improve tremor but are not as useful for bradykinesia or rigidity, and often have anticholinergic effects such as mental dullness, dry mouth, dry eye, and urinary hesitancy, especially in the elderly, so they have a limited role in Parkinson treatment.

■ MOTOR COMPLICATIONS: FLUCTUATIONS AND DYSKINESIAS

Motor fluctuations are changes between the akinetic and mobile phases of Parkinson disease, or the off-periods and on-periods of drug treatment. A patient who is “off” is generally rigid and feels that the medication is not working. A patient who is “on” feels loose and mobile and that the medication is working. Variants of motor fluctuations include:

- End-of-dose deterioration
- Delayed onset of response (more than half an hour after taking medication)
- Drug-resistant offs—medication has become ineffective
- Random oscillation—on-off phenomenon
- Freezing—unpredictable inability to start or finish a movement.

Dyskinesias are abnormal involuntary movements such as writhing and twisting. They are associated with dopaminergic therapy at peak dose, when the drug starts to turn on or wear off (termed *diphasic dyskinesias*).¹⁶

The storage hypothesis provides a plausible explanation for the development of motor complications as the disease progresses. Although the half-life of levodopa is only 60 to 90 minutes, it is effective in early disease when given three times a day. It is believed that at this stage of the disease, enough dopaminergic neurons survive to “store” dopamine and release it as needed. As the disease progresses and dopaminergic neurons die, storage capacity diminishes, and the clinical effect slowly starts to approximate the pharmacokinetic profile of the drug. Upon taking the medication, the patient gets a surge of drug, causing dyskinesias, followed later by rigidity as the effect wears off since there are fewer surviving dopaminergic cells to store dopamine.

When gait problems develop, treatment should be started

■ **MANAGING DYSKINESIAS**

Patients with dyskinesias should first be asked if they are bothered by them; not all patients are troubled by dyskinesias. If the movements only bother others (eg, family members), then education is often the only treatment needed. If the patient is uncomfortable, the following measures can be tried:

- Taking lower, more frequent doses of levodopa (however, risk of wearing off becomes a problem)
- Adding a dopamine agonist or MAO-B inhibitor while lowering the levodopa dose (however, MAO-B inhibitors pose a risk of side effects in elderly patients)
- Adding clozapine (periodic laboratory testing is required to monitor blood levels

and liver and kidney function)

- Adding amantadine (however, this poses a risk of cognitive side effects).

Deep-brain-stimulation surgery is appropriate for select patients who are generally physically healthy, cognitively intact, and emotionally stable, with a strong family support system, but who are bothered by symptoms of parkinsonism (such as tremors), motor fluctuations, or dyskinesias.¹⁷

Infusion pump. In January 2015, the FDA approved a new system that continuously delivers levodopa-carbidopa in a 4:1 ratio in gel suspension for 16 hours directly into the small intestine, minimizing motor fluctuations. The patient changes the cartridge daily and turns it off at bedtime. ■

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