



**Ockham Technical Synopsis** is a recurring series prepared for internal staff and consultants of Ockham Development Group Inc. (Ockham). Highlighting current and emerging issues and challenges in clinical research, these publications are intended to disseminate intelligence captured during the execution of key clinical trials and are therefore updated on a continuous basis.

## PARKINSON'S DISEASE (PD)

### INTRODUCTION

After Alzheimer's Disease, Parkinson's Disease is the most common neurodegenerative disease. It is a chronic, progressive disease that results when nerve cells in a part of the midbrain – the *substantia nigra* – die or are impaired. These nerve cells produce dopamine, an important chemical messenger that transmits signals from the *substantia nigra* to another part of the brain called the corpus striatum. These signals allow for coordinated movement. When the dopamine-secreting cells in the *substantia nigra* die, the other movement control centers in the brain become unregulated. These disturbances in the control centers of the brain cause the symptoms of PD. When 80% of the dopamine-producing cells in the *substantia nigra* are depleted, symptoms of PD develop.

First described in 1817 by British physician Dr. James Parkinson, PD is characterized by four major features:

- Rest tremor of a limb (shaking with the limb at rest)
- Slowness of movement (bradykinesia)
- Rigidity (stiffness, increased resistance to passive movement) of the limbs or trunk
- Poor balance (postural instability).

A diagnosis of PD is made when at least two of these symptoms are present, and especially if they are more evident on one side than the other (unless there are atypical features that suggest an alternative diagnosis). Patients may first realize something is wrong when they develop a tremor in a limb; movements are slowed and activities take longer to perform; or they experience stiffness and have balance problems. Initially, symptoms are a variable combination of tremor, bradykinesia, rigidity and postural instability. Symptoms typically begin on one side of the body and spread over time to the other side.

Changes occur in facial expression, so that there is a certain facial fixity (blank expression showing little emotion) or a staring appearance (due to reduced frequency of eye blinking). Complaints of a frozen shoulder or foot drag on the affected side are not uncommon. As symptoms come on gradually, older patients may attribute these changes to aging. The

tremor is thought to be “shakiness,” bradykinesia is regarded as normal “slowing down,” and stiffness is attributed to arthritis. The stooped posture, common to PD, may be attributed to age or osteoporosis. Both younger and older patients may experience initial symptoms for a year or more before seeking medical evaluation.

The characteristic symptom-complex of PD (tremor, rigidity, bradykinesia, postural instability) is termed parkinsonism. This is a general term and not all patients with parkinsonism have typical PD. Early in the disease process it may be difficult to know whether a patient has typical PD or a syndrome that mimics it. The development of additional symptoms and the subsequent course of the disease generally points to the correct diagnosis, which generally requires examination by a neurologist to distinguish between them.

PD affects 1 in 100 people over the age of 60, with the average age of onset being 60 years. It can also affect younger people. Young-onset PD (onset at age 40 or younger) is estimated to occur in 5%-10% of patients with PD.

### DISEASE PROGRESSION

Initially the symptoms are mild, usually on one side of the body, and may not require medical treatment. Rest tremor is a major characteristic of PD, and the most common presenting symptom, but some patients never develop it. Tremor may be the least disabling symptom, but is often the most embarrassing to the patient. Patients may keep their affected hand in their pocket, behind their back, or hold something to control the tremor, which may be more psychologically distressing than any physical limitation that it imposes.

Over time, initial symptoms become worse. A mild tremor becomes more bothersome and more noticeable. Bradykinesia becomes a significant and the most disabling symptom. Walking is slower and there is a stooped posture, with the head and shoulders hanging forward. The voice becomes soft and monotonous. A disturbance of balance may lead to falls. Handwriting becomes small (“micrographia”) and illegible. Automatic movements, such as arm swing when walking, are reduced.

Symptoms may originally be restricted to one limb, but will typically spread over time to the other limb on the same side. They eventually progress to the other side of the body. Generally this progression is gradual, but the rate of progression varies in different patients. As symptoms progress, it is important for patients to talk with their physicians so that optimal treatment can be established. The goal of treatment is not to abolish symptoms, but rather to help the patient manage their symptoms, function independently, and make the appropriate adjustments to a chronic illness. The illness

will not go away, but management of its symptoms can be successful in reducing disability or other handicap.

Patients are aware of the progressive nature of the illness and this may become a source of much anxiety. It is not uncommon for patients to over-monitor themselves and their symptoms, compare themselves to other PD patients whom they may meet (length of diagnosis, level of symptoms, etc.), and avoid situations such as support groups, where they may see patients who are worse off than they are. Concern about the progression of the disease and the ability to continue working is frequently voiced.

It is not possible to predict with any confidence the likely course of the disease in an individual patient. The rate of progression and resulting level of disability vary in different patients. Some guide to the likely outcome in individual patients is provided by the course of the illness since diagnosis, but this is no more than suggestive.

When the disorder is such that normal activities of daily living are impaired, at least to some extent, symptomatic treatment is begun.

---

#### INCIDENCE

There is a family history of PD in 5%-10% of patients. It may affect people of the same generation (e.g., a brother or sister) or in two generations, such as a father and son.

Environmental toxins such as manganese, carbon monoxide, and, rarely, certain pesticides cause diseases that resemble PD. However, most people with PD have not been exposed to these toxins. In less than 1% of cases, PD is clearly familial.

Several gene mutations have been shown to cause PD in a few families, but these have not been found in most individuals with PD. Studies of identical twins in which one twin was known to have PD showed no increase in the incidence of PD in the other twin compared to the general population of patients over the age of 60 years. However, among identical twins younger than 50, if one member of the twinship has PD, there is an increased risk of PD in the other twin. This indicates heredity may play a role in young-onset cases. Currently, researchers suspect that the cause of PD in most individuals reflects a combination of genetic factors and environmental exposures.

---

#### TREATMENT

At this time no treatment has been shown to slow or stop the progression of PD. Instead, therapy is directed at treating the symptoms that are most bothersome to an

individual with PD. For this reason, there is no standard or "best" treatment for PD. Treatment approaches include medication and surgical therapy.

The introduction of levodopa (or L-dopa) treatment over three decades ago revolutionized treatment of the disease.

Levodopa is available as a standard (or immediate) release formulation or a long-acting or "controlled-release" formulation. Over the years, a number of substitutes for levodopa have been developed. Unlike levodopa, these medications do not have to be modified by brain enzymes in order to activate dopamine receptors. As a class, these medications are called dopamine agonists and may be used in place of levodopa or in combination with it.

A number of other medications can be used alone or in combination with levodopa or a dopamine agonist to improve movement for people with PD. The most commonly used medications are: amantadine, anticholinergic medications, and selegiline.

#### Commonly Prescribed Medications

##### Levodopa

###### *Standard-Release Preparations:*

- levodopa/carbidopa (Sinemet® or Atamet®)
- levodopa/benserazide (Madopar®<sup>1</sup>)

###### *Extended-Release Preparations:*

- levodopa/carbidopa (Sinemet CR®)
- levodopa/benserazide (Madopar HBS®)

##### COMT Inhibitors

- entacapone (Comtan®<sup>2</sup>)
- tolcapone (Tasmar®<sup>3</sup>)

##### Dopamine Agonists

- bromocriptine (Parlodel®)
- pergolide (Permax®)
- pramipexole (Mirapex®)
- ropinirole (Requip®)
- cabergoline<sup>4</sup> (Dostinex®)
- apomorphine (Apokyn®)
- lisuride<sup>1</sup> (Dopergine®)

##### Amantadine

- Amantadine (Symmetrel®)

---

<sup>1</sup> not currently available in the U.S.

<sup>2</sup> available in the U.S. and other countries

<sup>3</sup> available in the U.S., but not Canada or Europe

<sup>4</sup> not currently approved in the U.S. for treatment of PD

Anticholinergics

- Biperiden HCL (Akineton®)
- Benztropine mesylate (Cogentin®)
- Procyclidine (Kemadrin®)
- Trihexyphenidyl (Artane®)

Selegiline

- Eldepryl®
- Atapryl®
- Carbex®

**Protective Treatments**

Current PD medications can significantly impact on the management of the disease. They do not, however, prevent its progression. There is great interest in the development of neuroprotective therapies to halt the disease or delay its onset. Cell loss in the *substantia nigra* is the cause of symptoms of PD. The reason that it occurs is unclear. The occurrence of certain chemical reactions involving oxidation results in the production of substances (such as so-called free radicals or reactive oxygen species) that may be harmful to cells and lead to their deaths. Such oxidative stress may thus be important with regard to the development of PD. Neuroprotective treatments may be most helpful at an early stage of PD, and this stresses the need for finding a simple biological marker. This would enable treatment to be initiated at the preclinical or early clinical phase of the disease.

**Levodopa:** There is controversy as to whether this medication is toxic to neuronal cells or protective. There is no evidence that it worsens or slows the progression of PD.

**Selegiline:** An inhibitor of the enzyme monoamine oxidase B (MAO-B). Since this enzyme breaks down dopamine, inhibiting it prolongs the action of dopamine in the brain and may improve the symptoms of PD. It also has a mild antidepressant effect. While early studies of selegiline initially led physicians to believe that it may delay the progression of PD, currently there is no firm evidence that this is so. Nevertheless, there are theoretical grounds to believe it may slow the disease.

**Coenzyme Q10:** A recent study suggested that treatment with 1200 mg/day of coenzyme Q10 resulted in less disability over the fixed period of the study than lower doses of the same compound or a placebo. A larger trial is needed to confirm these findings and to determine the optimal dose of coenzyme Q-10 to use. Patients are not advised to start taking large doses of coenzyme Q-10 at this time.

**Dopamine agonists:** Have been shown experimentally to protect dopamine cells. They may have antioxidant effects, inhibiting free radical formation and scavenging

free radicals. They may also slow programmed cell death (apoptosis) which may be accelerated in PD.

**Experimental Treatments**

Many patients inquire about "restorative" therapies, a category of procedures that includes transplantation of fetal cells or stem cells, growth factors, or gene therapy. The goal of these procedures is to correct the basic chemical defect of PD by increasing the production of dopamine in the brain. Although theoretically very attractive, much more laboratory work must be done in order to make cell transplantation or growth factor therapies practical and effective. At this time, the restorative therapies are experimental and are not available as treatment.

**RECENT INDUSTRY-SPONSORED PHASE I-III STUDIES (ENROLLMENT RATES)**

<i>Trial</i>	<i>PD Diagnosis</i>	<i>Sites</i>	<i>Patients</i>	<i>Enrollment Rate</i>
1	Early	26	335	1.288
2	Early	20	264	1.886
3	Early	25	360	1.309
4	Early	4	55	1.058
5	Advanced	9	69	0.426
6	Advanced	6	50	0.556
7	Advanced	10	77	0.513
8	Late-Stage	22	56	0.212
9	Late-Stage	26	64	0.205