

M. Carranza
M. R. Snyder
J. Davenport Shaw
T. A. Zesiewicz



Parkinson's Disease

A Guide to Medical Treatment



© **SEEd srl**. All rights reserved
Piazza Carlo Emanuele II, 19 – 10123 Torino, Italy
Tel. 011.566.02.58 – Fax 011.518.68.92
www.edizioniseed.it
info@edizioniseed.it

First edition
May 2013
ISBN 978-88-9741-942-6

Although the information about medication given in this book has been carefully checked, the author and publisher accept no liability for the accuracy of this information. In every individual case the user must check such information by consulting the relevant literature.

This work is subject to copyright. All rights are reserved, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilm or in any other way, and storage in data banks. Duplication of this publication or parts thereof is permitted only under the provisions of the Italian Copyright Law in its current version, and permission for use must always be obtained from SEEd Medical Publishers Srl. Violations are liable to prosecution under the Italian Copyright Law.

Table of Contents

1	EPIDEMIOLOGY, DIAGNOSIS, AND PATHOPHYSIOLOGY OF PARKINSON'S DISEASE.....	7
1.1	A Brief History of Parkinson's Disease.....	8
1.2	Clinical Features of Parkinson's Disease.....	9
1.3	Epidemiology of Parkinson's Disease	15
1.4	The Neurochemistry of Parkinson's Disease	17
1.5	Pathophysiology of Parkinson's Disease	25
1.6	Diagnosing Parkinson's Disease	28
1.7	The Stages of PD	34
	References	37
2	PHARMACOLOGY OF TREATMENTS FOR PARKINSON'S DISEASE MOTOR SYMPTOMS.....	49
2.1	Levodopa and Levodopa/Carbidopa	50
2.2	Dopamine Agonists	65
2.3	Catechol-O-Methyltransferase (COMT) Inhibitors	88
2.4	Anticholinergic medications	102
2.5	Amantadine (Symmetrel®, Symadine®)	108
2.6	Monoamine Oxidase B (MAO-B) Inhibitors	113
	References	123
3	MEDICAL MANAGEMENT OF MOTOR SYMPTOMS OF PARKINSON'S DISEASE.....	141
3.1	Management of Early Parkinson's Disease	141
3.2	Treatment of Advancing Parkinson's Disease: Levodopa Rescue....	155
3.3	Management of Advanced Parkinson's Disease: Complications of Therapy.....	157
3.4	Considerations for the Management of Hospitalized Patients With Parkinson's Disease	180
3.5	Conclusion	182
	References	187

4	TREATMENT OF NEUROPSYCHIATRIC SYMPTOMS IN PD	203
4.1	Treatment of Depression and Anxiety	203
4.2	Treatment of Dopaminergic-induced Psychosis	224
4.3	Treatment of Impulse Control Behaviors	231
4.4	Treatment of Cognitive Impairment and Dementia in PD.....	234
	References	243
5	CLINICAL TREATMENT OF DYSAUTONOMIA IN PD	253
5.1	Orthostatic Hypotension	253
5.2	Sexual Dysfunction	259
5.3	Constipation	261
5.4	Sialorrhea	266
5.5	Abnormal Sweating (Dyshidrosis)	270
5.6	Urinary Incontinence.....	271
	References	272
6	CLINICAL TREATMENT OF SLEEP DISORDERS IN PD.....	279
6.1	Insomnia	279
6.2	Treatment of Excessive Daytime Somnolence and Sleep Attacks ...	286
6.3	Treatment of Restless Leg Syndrome and Periodic Limb Movements of Sleep.....	288
6.4	Treatment of REM Sleep Behavior Disorder	296
	References	299
7	CLINICAL TREATMENT OF NON-MOTOR SYMPTOMS, SENSORY ABNORMALITIES AND FATIGUE	309
7.1	Treatment of Pain in PD.....	310
7.2	Treatment of Fatigue in PD	315
	References	317
8	PATIENT Q&A: 25 QUESTIONS ABOUT PD AND THE CLINICAL MANAGEMENT OF ITS MOTOR AND NON-MOTOR SYMPTOMS....	321
8.1	How fast does PD progress? What can I expect in the coming years in terms of mobility?	321
8.2	I recently was diagnosed with PD. Can my adult children get PD? ...	322

8.3	Are generic medications different from brand names? Can I use them?	322
8.4	How often should I be seeing my physician for PD?.....	323
8.5	Should I have a primary care physician?	323
8.6	I am a female who was recently diagnosed with PD, and I have a long history of oral contraceptive use. A friend told me she read that birth control use may put you at higher risk for developing PD. Is this true?	324
8.7	What are some future treatments for PD? Does stem cell therapy play a role?	325
8.8	What is gene therapy?	328
8.9	What surgical treatment options are available for patients with PD? Are all PD patients candidates for surgery?.....	328
8.10	My doctor told me that he feels I would benefit from DBS. Are there any risks from the surgery I should be aware of?	329
8.11	What symptoms of PD does Botox® help to manage?	330
8.12	My energy level has been low, and I find myself taking many naps during the day. Is this a side effect of a medication I am on, or is it due to my disease?	331
8.13	How effective is available treatment for restless leg syndrome?	331
8.14	I experience chronic pain. What treatments are available for pain associated with PD?	332
8.15	What natural supplements, if any, should I be taking with PD?	333
8.16	Should I take vitamins with PD?	336
8.17	I was recently diagnosed with PD. Are there certain changes I should make to my diet?	337
8.18	What is pet therapy?	338
8.19	Is physical therapy good for me? What are the best types? What about Tai Chi?	338
8.20	I used to do yoga when I was younger, and my physician mentioned to me that there is a yoga class offered in the clinic for patients. Have there been any studies that show yoga is beneficial for PD patients?.....	339
8.21	Some of my friends get acupuncture. Should I look into this as an option?.....	340
8.22	Would regular exercise improve my level of fatigue?	341

8.23	How can I improve my home so that I am less likely to hurt myself?.....	342
8.24	I have PD and I am having trouble with my balance. My physician recommended I purchase a walking device. How do I choose the best one?	342
8.25	Where can I go online to find out more about PD?.....	343
	References	343
	AUTHORS	353

1 Epidemiology, Diagnosis, and Pathophysiology of Parkinson's Disease

Parkinson's disease (PD) is a progressive neurological disorder of the central nervous system, caused by the degeneration of dopamine neurons within the basal ganglia. When roughly 80% of dopamine has been depleted, deficits in the motor neuron circuitry manifest in the cardinal symptoms of the disease, which include tremor, rigidity, bradykinesia or slow movement, and postural instability. Proper identification and treatment of both motor and non-motor symptoms lead to a better overall quality of life, reducing stress incurred by both patient and caregiver.

This chapter will provide an introduction to the historical prominence of Parkinson's disease, clinical and epidemiological characterizations, the role of dopamine within the motor circuitry, and the pathophysiologic evidence.



Figure 1.1. Dr. James Parkinson.

1.1 A BRIEF HISTORY OF PARKINSON'S DISEASE

James Parkinson (1755-1824) was a nineteenth century English physician and apothecary whose acute observations in neurology led to the official distinction of the disease which bears his name. In his 1817 "An Essay on the Shaking Palsy" [1], Parkinson described six cases of what had been previously classified as the "shaking palsy." Parkinson detailed the gradual progression of disability marked by increasing tremor severity, deteriorating articulation, sleep disturbances, difficulty with self-feeding, as well as the inability to walk, write or use the bathroom without assistance. The symptoms of tremor, festination, and autonomic dysfunction were all previously thought to have been manifestations of separate pathological entities. However, Parkinson conjectured that these symptoms were indicative of a single pathology, and highlighted the importance of being able to distinguish this disease from others that resemble it. Although Parkinson was the first to combine historical observations into an accurate description of the disease in the context of its cardinal features, it was not until some sixty years after his death that the French neurologist Jean-Marie Charcot attributed his name to the condition in 1884 [2].

Prior to the nineteenth century, few neurological signs and symptoms had been differentiated into distinct pathological etiologies [3]. Rather, physicians published their observations for others to consider during practice. Parkinson's diagnostic acumen in describing the "shaking palsy" allowed physicians to identify a neurological disease that had perhaps been detailed by numerous medical professionals for millennia. It is difficult to certify whether these previous descriptions can be definitively classified as symptoms of Parkinson's disease [4]. However, scholarly analyses suggest that these observations may in fact represent the earliest documentation of the myriad of clinical correlates that are characterized as "parkinsonism" [4].

While James Parkinson was the first to put the symptoms of Parkinson's disease together under a single diagnosis, he did give credit to earlier physicians as having recognized many of the individual symptoms. In his 1817 essay, James Parkinson cited numerous physicians that detailed several symptoms of the "shaking palsy" that he described, including action and rest tremor, as well as gait and speech disturbances [1]. Parkinson credited the Dutch physician Franciscus Sylvius de la Boe (1680), who along with the Dutch-Austrian physician Gerard van Swieten, differentiated between involuntary tremor during voluntary actions and while at rest [3-5]. German physician Gaubius (1758) was also cited for his report on the clinical triad of tremor, speech disturbance and festinating gait [6]. The French scientist Boissier de Sauvages also described muscular rigidity and compulsive tremor in his 1768 volume of disease classification: "the shaking limbs jump even when they are being supported, just as if they are being agitated, so that no relaxation is possible at all" [7]. Charcot is often cited for his distinction between rigidity and bradykinesia [8].

1.2 CLINICAL FEATURES OF PARKINSON'S DISEASE

There are four cardinal features of PD, which can be grouped under the acronym TRAP: Tremor at rest, Rigidity, Akinesia (or bradykinesia), and Postural instability [9]. Flexed posture and freezing (motor blocks) are also typical motor symptoms of PD [9]. In addition to the secondary motor symptoms described below, non-motor symptoms are common in PD patients and of critical importance during the management of the disease.

The onset of PD symptoms is typically insidious and asymmetric, worsening with age and disease severity. Since James Parkinson first described the constellation of PD symptoms that fall under

the clinical umbrella of “parkinsonism,” researchers have identified many new symptoms in association to the underlying degeneration of dopaminergic and non-dopaminergic neurons. As dopamine levels decrease over time, other neurotransmitter systems may become involved and induce the development of symptoms unrelated to decreased levels of dopamine. Collectively, the clinical spectrum of symptoms may be segregated into motor and non-motor symptoms.

Motor Symptoms

Motor symptoms are often the first to be observed in patients with PD [10]. Rest tremor, bradykinesia, rigidity and postural instability are clinical hallmarks of motor impairment in PD. These signs and symptoms are directly correlated to dopaminergic neuron loss in the striatum and substantia nigra [11]. Secondary motor manifestations of PD include akathisia, decreased arm swing during walking, freezing phenomenon, ophthalmologic abnormalities (decreased blink rate, ocular surface tension, altered tear film, hallucinations, blepharospasm and decreased convergence, apraxia of eyelid opening, and limited upward gaze), as well as the re-emergence of primitive glabellar and palmomental reflexes [9,12-17].

Tremor

Tremor at rest is often the first observed symptom in PD and is distinguished from other forms of tremor (namely essential tremor) by its unilateral and supination-pronation nature, also known as “pill-rolling.” It has been reported that approximately 69% of patients with PD have rest tremor at disease onset, with 75% having tremor during the course of their disease [18,19]. Studies have reported that degeneration of a subgroup of midbrain neurons is found in PD patients with significant tremor, but spared in PD patients without tremor [9]. Rest tremor in PD may at first be provoked

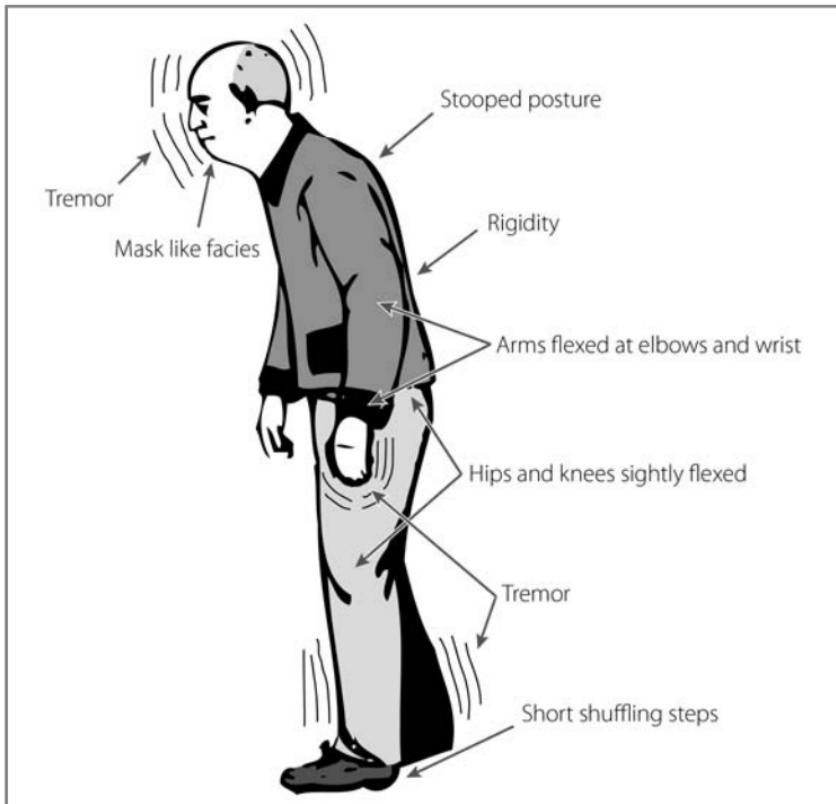


Figure 1.2. Illustration of common motor symptoms in patients with Parkinson's disease.

by stress, but typically becomes less intermittent [11]. It eventually affects the contralateral limbs with advancing disease, although not typically to the same extent as in the original limb [11]. PD patients may also experience a form of delayed postural tremor called "re-emergent" tremor, elicited by asking the patient to outstretch their arms on a horizontal plane [20].