Emerging Drugs and Targets for Parkinson's Disease

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Preface

"Now this is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning."

Sir Winston Churchill

Despite the great goals achieved in our era, such as reaching the moon or finding the Higgs particle among others, human health remains fragile and our current therapeutic arsenal is completely insufficient to cure many severe diseases. Drug discovery today is fueled by the urgent need to find effective drugs for many unmet pathologies.

Parkinson's disease, the second most common neurodegenerative disorder, is one of the above mentioned pathologies. Following the death of dopamine-generating cells in the *substantia nigra*, it is characterized by progressive loss of muscle control, which leads to trembling of the limbs and head while at rest, stiffness, slowness, and impaired balance. As symptoms worsen, it may become difficult to walk, talk and complete simple tasks. The first descriptions of Parkinson's disease date back as far as 5000 BC. Around that time, an ancient Indian civilization called the disorder 'Kampavata' and treated it with the seeds of a plant containing therapeutic levels of what is today known as levodopa. The disease is named after the British doctor James Parkinson, who published its first detailed description in *An Essay on the Shaking Palsy* in 1817.

Although more than 5 million people worldwide are affected by Parkinson's disease, currently there is no treatment to cure this mid-brain neurodegenerative pathology. Several therapies are available to delay the onset of motor symptoms, and to ameliorate motor symptoms, thereby extending the patient's quality of life.

Recent research advances in molecular biology and technology have provided multiple credible hypotheses around which therapeutic agents can be developed. This book collects some of the most outstanding examples of new

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drugs currently under pharmaceutical development or new targets in the validation process that will reach the Parkinson's drugs market over the next few years as disease-modifying drugs. These new drugs will be able to provide effective treatment for motor and non-motor symptoms.

We wish to thank all of the contributors to the chapters in this book, firstly for their faith in the project, and we would like also to express our great appreciation to all of them for delivering clear, comprehensive reviews that will inform and enlighten readers on the state-of-the-art in their respective fields of research. We would also like to thank our families and students for their patience when we were immersed in editing, and the staff at the RSC, especially Gwen Jones and Cara Sutton, for their support in bringing the book to completion. It is very much hoped that this book will provide a useful resource to scientists, both in industry and academia, who are looking to find a solution for the many patients worldwide waiting for effective drugs.

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Introduction

CHAPTER 1

Parkinson's Disease: Symptoms, Unmet Needs and New Therapeutic Targets

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1.1 Introduction

Since James Parkinson wrote the first systematic clinical description of six patients in 1817 in his essay titled "Paralysis Agitans",[1] Parkinson's disease (PD) has been considered a motor disorder, consisting of tremor, rigidity and gait difficulties. A few decades later, Jean Martin Charcot characterized the feature of bradykinesia and added other observations not pertaining to the motor domain, consisting of arthropathy, dysautonomia, and pain.[2] In the mid 1950s, pathological changes in the PD mid-brain described as "neuronal degeneration of the *substantia nigra*" were defined by Greenfield and Bosanquet.[3] The delineation of the nigrostriatal pathway in the 1960s and discovery by Arvid Carlsson and colleagues of the direct correlation between

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striatal dopamine loss and clinical Parkinsonian manifestations were a major breakthrough in the neurosciences and provided the opportunity for the development of effective therapies.[4] In 1967 George Cotzias and others demonstrated the benefits of oral levodopa in patients, paving the way for substitutive dopaminergic treatments.[5,6]

1.2 Motor Signs and Symptoms

Based on these early findings, the classic features that define the Parkinsonian syndrome are: bradykinesia, rigidity, tremor at rest, and gait disturbances (flexed posture, freezing, and loss of postural reflexes). At least two of these signs should be present before the diagnosis of Parkinsonism is put forth.[7] The etiology is widely variable, therefore multiple primary and secondary causes must be considered when evaluating a patient, considering that PD is the most prevalent of the primary causes. In the following section, the well-established PD motor symptoms are enumerated and defined (Table 1.1).

1.2.1 Bradykinesia

The terms akinesia, literally means absence; bradykinesia, meaning slowness; and hypokinesia, meaning decreased amplitude; are all used, often interchangeably, to describe the most prominent phenomena of Parkinsonism. Patients show poverty of automatic movements (*i.e.*, blinking, arm swing) and also present reduced speed when initiating and executing single and repetitive movements with progressive loss of amplitude. Characteristically, there is greater difficulty in moving with self-initiated cues than with externally triggered movements and this abnormal activation and slowness affects most body parts.

Pathophysiology of bradykinesia can generally be explained by the classic model of the basal ganglia–thalamocortical circuitry postulated in the 1980s. In the absence of dopamine, the main output nucleus of the basal

Table 1.1 The motor symptom and sign complex of PD.

Axial symptoms	*Limb symptoms*
Hypomimia	Micrographia
Blepharospasm	Loss of dexterity
Hypophonia	Asymmetric arm swing
Dysarthria	Slow gait
Dysphagia	Rest tremor of the hand or foot
Sialorrhea	Foot dystonia
Chin, lip and tongue tremor	
Vertical eye movement restriction and convergence insufficiency	
Freezing of gait	
Flexed posture	
Loss of postural reflexes	
Camptocormia	

ganglia, the *globus pallidus interna* (GPi) is abnormally active, thus inhibiting the ventroanterior and ventrolateral motor thalamus, and subsequently the primary motor cortex, resulting in slowness. Current findings add complexity to the model, attempting to explain the other features of akinesia. It is hypothesized that the main disturbances in PD are the non-generation of phasic neurons, and the time-locked inhibition of GPi neurons which cannot facilitate recruitment of cortical motor neurons that are appropriately adjusted to produce voluntary movement. The primary motor cortex is also altered and there is a functional uncoupling with premotor areas that is not well understood. The loss of automatic movements in PD is probably related to alterations of basal ganglia projections to the brainstem central pattern generators, with excessive inhibition being the net result.[8]

1.2.1.1 Hypomimia

Bradykinesia affecting the facial muscles results in decreased expression, sometimes called 'poker' face, alluding to card players that do not show any emotion during their game, and can be an initial sign of the disease. This sign can also be seen in depressed patients and the differential diagnosis must be kept in mind. With disease progression, the lips can remain open most of the time and blink rate becomes severely decreased, leading to ocular problems such as dry eye.

1.2.1.2 Hypophonia

Hypophonia, meaning soft voice, is an axial sign that can also be a first complaint and is generally noted by the patient's family and friends. The person with PD is usually unaware that he/she is speaking softly and tends to blame others for being 'hard of hearing'. Some patients complain that their tone of voice has changed and become monotonous (termed ''aprosody'').

1.2.1.3 Dysarthria

Difficulty in articulating language is a reflection of bradykinesia of the tongue, oral cavity and larynx musculature. Some patients may talk too fast, presenting tachyphemia, others may stutter, due to freezing of speech episodes, and in advanced stages of the disease, patients may develop progressively severe mumbling that can make language unintelligible.

1.2.1.4 Dysphagia

Difficulty swallowing secondary to neurological disease generally affects liquids more than solids. Patients complain of coughing during their meals due to minor choking episodes and with disease progression, dysphagia may be severe and lead to aspiration, causing pulmonary infections such as pneumonia. In order to avoid this, patients must be instructed to maintain proper posture

when swallowing and avoid food textures, liquids and volumes they have difficulty managing. Ultimately, gastrostomy may be considered although the danger of saliva aspiration is not avoided.

1.2.1.5 Sialorrhea

Excessive salivation is probably secondary to decreased spontaneous swallowing although in some patients, saliva characteristics can differ from normal (becoming denser), and thus hypersalivation may also be considered a non-motor dysautonomic problem.

1.2.1.6 Eye Movement Abnormalities

In the past two decades, neuro-ophtalmologic symptoms in PD have been objectively measured and thus defined. Horizontal and vertical pursuit can show bradykinesia and decreased amplitude even in the early stages of the disease[9] and as in other body parts, slowness becomes increasingly marked with repetition.[10] It is not infrequent to find restriction of vertical eye movements. The saccade system is also altered, showing characteristically slow and hypometric saccades, and occasionally prolonged latencies.[11,12] Patients often complain of blurred or double vision, secondary to convergence insufficiency as Biousse *et al*. found in an early untreated PD cohort.[13] This study also showed that, when compared to controls, PD patients declared more local ocular symptoms (irritation, pain, conjunctival redness), eyelid problems (blepharospasm and decreased blinking) and dry eye.[13] Dry eye is probably multi-factorial, secondary to motor disturbances (decreased blinking), and dysautonomic changes of the lacrimal glands.[14]

1.2.1.7 Micrographia

Small handwriting can often be the first symptom noted when PD affects the dominant side of the body. Patients describe that their writing starts out normally but becomes increasingly smaller as they keep writing. Their handwriting can become illegible and their signature can change to the point of misunderstandings with banks and official documents.

1.2.1.8 Slow Gait

Some patients' initial complaint is that they walk more slowly. They describe walking as tremendously effortful, since their legs feel heavy, as if they had weights pulling them down. Often a person close to them will note that they have decreased arm swing, usually asymmetric. Recent studies show that there are marked alterations in the rhythmicity and timing of gait, even in the early stages of the disease when speed can be intact.[15]

1.2.2 Rigidity

Rigidity is defined as increased muscle tone at rest that can be palpated, reduced distension when the limb is passively moved, increased resistance when the limb is stretched, and facilitation of the shortening reaction.[8] Resistance is more noticeable when the limb is passively moved slowly, can manifest as cog-wheeling since the limb gives way in a stepwise fashion, and is increased with voluntary movement of other body parts (Froment's maneuver). Flexor muscles are generally affected earlier than the extensors. Rigidity is not explained by the classic model of the Parkinsonian state, where overactivity of the basal ganglia's main output nucleus (GPi) leads to cortical inhibition. Projections to the brainstem and spinal mechanisms probably play an important role as experimental findings suggest that spinal cord motorneurons present a shift towards increased activity in response to peripheral stimulation.[8]

1.2.3 Rest Tremor

Parkinsonian tremor usually involves distal parts of the extremities (called "pill rolling" when the thumb and index are involved) or the lips and chin, and characteristically occurs at rest. About two thirds of patients with PD show the typical rest tremor with a frequency measured by motor neurophysiological testing (electromyography and accelometery) of 4–5 Hz. Some rest tremors re-emerge after a short latency period of a few seconds, thus appearing during some actions such as posture holding. Kinetic and postural tremors can also be seen, but are generally not significant and do not interfere with the patient's activities. The pathophysiological mechanism behind PD tremor is unclear. To date there is no proven model that explains the link between dopamine deficiency and abnormal oscillatory activity in an extensive motor network that involves the basal ganglia, the cerebellum, the thalamus and the motor cortex.[8]

1.2.4 Gait Disturbances

1.2.4.1 Freezing of Gait

When initiating gait or turning, the feet literally become stuck to the ground, so the patient feels he/she cannot take a step. Some patients may present freezing in the initial stages of the disease, although it is rare in the first three years. The problems begin when they want to initiate gait (start hesitation), when turning, in tight spaces, or in doorways. With disease progression, patients develop destination freezing (*i.e.*, stopping a few steps from the chair where they want to sit) and freezing may interrupt gait at any time, even in open spaces. Characteristically patients with freezing do not have trouble with other complex motor programs such as climbing stairs or riding a bicycle. To date, the physiopathology of freezing is not well understood and the best treatment for freezing is based on physiotherapy since most patients benefit from external visual or auditory cues.

1.2.4.2 Flexed Posture

As the disease advances, patients tend to walk with flexion at the neck, elbows, hips and knees, with the forearms placed in front of the body. When extreme, this flexed posture can lead to pronounced kyphoscoliosis.

1.2.4.3 Loss of Postural Reflexes

Balance is tested in the office by a gentle pull backwards on the shoulders by the examiner. In the early stages of the disease, patients may have to take a few steps backwards (up to two is considered normal) in order to regain their balance. As the disease progresses, patients will not be able to recuperate due to loss of postural reflexes and falls become a major problem.

1.2.4.4 Festination

The patient with a festinating gait walks progressively faster and faster, taking shorter and shorter steps as he/she tries to catch up with his/her axial center of gravity. It is a result of stooped posture and altered postural reflexes.

1.2.4.5 Falls

One of the symptoms with highest morbidity in PD is falling, conditioned by multiple factors. Freezing is one of the primary etiologies of falls, as the body moves forward or to the side when turning, but the feet do not follow. Festinating gait can also cause the patient to fall forward as eventually the lower limbs cannot catch up with the forward tilting trunk. Loss of postural reflexes means that any small obstacle or nudge will throw the patient off balance, generally leading to a fall backwards. Cognitive impairment also plays a role in patients' falls, since loss of insight and risk appraisal can be affected.

1.2.5 Motor Fluctuations and Dyskinesias

With disease progression, treated patients may develop motor fluctuations, signifying they present what is termed an "off" state, in which their motor symptoms re-appear as medication benefits disappear, and an "on" state, when medications are effective and symptoms are well controlled. In addition to this, they may develop dyskinesias or involuntary movements that resemble chorea or dancing movements, generally appearing in the areas most affected by parkinsonism and probably secondary to dopamine receptor hypersensitivity.

1.2.6 Dystonia

Abnormal posturing due to sustained muscle contractions can be the first sign of the disease, or it can develop years later as a consequence of dopaminergic treatment, representing a similar phenomenon to dyskinesias. Axial dystonia

can affect the eyes, causing blepharospasm; the neck, usually producing antecollis; or the trunk, resulting in camptocormia or stooped posture that increasingly worsens with walking, or Pisa syndrome, as patients lean the trunk to the side. Axial dystonia characteristically normalizes when standing against a wall or lying down. Secondary dystonia of the limbs can be associated with tremor (dystonic tremor), which tends to be faster and more erratic than the typical 4–5 Hz rest tremor, and when affecting the lower extremities can lead to abnormal gait.

1.3 Non-Motor Symptoms

At present, PD is still defined clinically by the presence of two or more of the cardinal motor symptoms described above. However, in the past decade, research has expanded to the prevalent non-motor symptom complex that affects patients during all stages of the disease, even in the premotor phase. Non-motor symptoms including sleep, mood, cognition, pain, and autonomic disorders have been identified as important PD manifestations, which often remain undeclared unless specifically sought.[16,17] It is important to recognize and treat these symptoms since they are key determinants of patients' quality of life. Results of a recent study by our group showed that non-motor symptoms have, as a whole, a greater impact on health-related quality of life (HRQoL) than motor symptoms, and non-motor symptom progression contributes importantly to HRQoL decline in PD patients.[18]

The neurochemical and pathological substrates for most of the non-motor symptoms remain a puzzle. Key dopaminergic areas in the brain (the *substantia nigra pars compacta*, ventral tegmental area, and hypothalamus) project extensively to form four main circuits: the mesocortical, meso-limbic, nigrostriatal, and tuberoinfundibular pathways, which mediate several non-motor symptoms such as cognition, sleep, and pain. Other non-dopaminergic pathways depending on neurotransmitters such as serotonin, norepinephrine and acetylcholine also play a major role.[19] Therefore, the non-motor symptoms that are classified and described in the next section may be modulated by dopaminergic therapy (Table 1.2) while others rarely respond.

1.3.1 Neuropsychiatric Symptoms

1.3.1.1 Depression

Depression is very frequent in PD patients, although prevalent cases range from 2.7 to 70%, depending on the study,[20] possibly due to differing methodologies. In practice, about 40% of patients[21] show signs of depression which can be expressed as sadness, but often presents as irritability, hopelessness, pessimism or worry, more often than guilt or remorse, and contributes to insomnia and general slowness. Studies have suggested that depression is probably another premotor non-motor biomarker that can precede the development of clinical PD as it is currently defined.[22–24] Serotoninergic