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Update in Parkinson's Disease

Fátima Carrillo and Pablo Mir
Unidad de Trastornos del Movimiento. Servicio de Neurología. Instituto de Biomedicina de Sevilla (IBiS). Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Spain

1. Introduction

Parkinson's disease (PD) was first described in 1817 by James Parkinson, who described in his monograph entitled "*An Essay on the Shaking Palsy*" the description of the clinical features of this disease (Parkinson, 1817). The cardinal clinical manifestations of PD are resting tremor, rigidity, bradykinesia, and gait dysfunction. It is now appreciated that PD is also associated with many nonmotor features, including autonomic dysfunction, pain and sensory disturbances, mood disorders, sleep impairment, and dementia (Olanow et al, 2009). PD is the second most common neurodegenerative disorder, with an average age at onset of about 60 years and the mean duration of the disease from diagnosis to death is 15 years, with a mortality ratio of 2 to 1 (Katzenschlager et al, 2008). The incidence of the disease rises steeply with age, from 17 - 4 in 100 000 person years between 50 and 59 years of age to 93 - 1 in 100 000 person years between 70 and 79 years, with a lifetime risk of developing the disease of 1 - 5% (De Rijk et al, 1995). With the aging of the population and the substantial increase in the number of at-risk individuals older than 60 years, it is anticipated that the prevalence of PD will increase dramatically in the coming decades (De Lau and Breteler, 2006).
The etiology remains obscure but important genetic and pathological clues have recently been found. This monograph is designed to make a comprehensive review of all aspects of both clinical as pathophysiological and therapeutic concerning PD, as well as an update on the innovative aspects of the disease primarily focused on identifying new genetic factors and new outlook therapeutics.

2. Neuropathology

Pathologically, PD is characterized by degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc). However, cell loss in the locus coeruleus, dorsal nuclei of the vagus, raphe nuclei, nucleus basalis of Meynert, and some other catecholaminergic brain stem structures including the ventrotegmental area also exists (Damier et al, 1999). This nerve-cell loss is accompanied by three distinctive intraneuronal inclusions: the Lewy body, the pale body, and the Lewy neurite. A constant proportion of nigral neurons (3–4%) contain Lewy bodies, irrespective of disease duration. This finding is consistent with the notion that Lewy bodies are continuously forming and disappearing in the diseased substantia nigra (Greffard et al, 2010). The brain-stem shape is a spherical

structure measuring 8–30μm with a hyaline core surrounded by a peripheral pale-staining halo, and is composed ultrastructurally of 7–20-nm wide filaments with dense granular material and vesicular structures. Pale bodies are large rounded eosinophilic structures that often displace neuromelanin and are the predecessor of the Lewy body.

Aggregated α-synuclein is the main component of Lewy bodies in dopaminergic neurons of all PD patients, including those in whom PD occurred sporadically. Aggregated α-synuclein in the cytosol of cells does not only occur in the Substantia nigra but already earlier, pre-symptomatically in the motor part of the Nucleus vagus, in the olfactory bulb and in the Locus coeruleus. In later stages cortical areas of the brain are also frequently involved (Braak and Tredici, 2010). In fact, these bodies are present in small numbers in almost all cases of PD (Halliday et al, 2008). Neocortical Lewy bodies are not necessarily the pathological correlate of dementia in PD (Colosimo et al, 2003; Parkkinen et al, 2005). The amount of associated cortical β-amyloid seems to be the key factor for the cognitive decline in PD (Holton et al, 2008; Halliday et al, 2008). The hypothesis that the aggregation of α-synuclein and the build up of Lewy bodies results in toxicity has been challenged.

Currently, most evidence indicates that oligomers but not the fibrils of α-synuclein that are deposited in the Lewy bodies, are the toxic species. This would also imply that the rapid conversion of α-synuclein from an oligomeric to an aggregated state, deposited in Lewy bodies, may help to detoxify the oligomeric form of α-synuclein (Goldberg and Lansbury, 2000). Fetal mesencephalic neurons implanted in patients with PD to restore dopaminergic transmission may develop Lewy bodies. The existence of different striatal level factors present in the striatal microenvironment of the host probably triggers the propagation of alpha- α-synuclein pathology. Inflammation, oxidative stress, excitotoxicity, and loss of neurotrophic support of the grafted neurons could all be important factors (Li et al, 2008, 2010). A prion hypothesis implicating permissive templating has also been proposed (Hardy 2005).

The few patients with PD of genetic origin (α-synuclein, *LRRK-2*, and *GBA* mutations) who have had autopsy have all shown changes indistinguishable from those found in patients with PD (Lees et al, 2008). Some families with *LRRK-2* mutations also have tangle pathology and non-specific neuronal loss (Gilks et al, 2005). In contrast, parkin mutations lead to nigral loss, restricted brain-stem neuronal loss, and absence of associated Lewy bodies or neurofibrillary degeneration. Heterozygous parkin carriers, however, have been associated with both Lewy body and neurofibrillary tangle pathology (Van de Warrenburg et al, 2001; Pramstaller et al, 2005).

3. Genetic of Parkinson's disease

The PD is mostly idiopathic. However, at present, genetics has taken a very important role in clinical diagnosis. The first genetic contribution to PD was made by William Richard Gowers, in 1902, with the observation of familial aggregation in some patients with PD, but it was not until 1997 that discovered the first gene mutation associated with it (*SNCA*/α–synuclein).

Today there are two kinds of Mendelian PD: autosomal dominant and autosomal recessive PD. Generally, the recessive autosomal forms are associated with PD onset age of juvenile (age of onset <40 years) and an unknown condition. Parkin (*PRKN*) is the most frequently mutated gene in early-onset PD. Dominant autosomal PD is later onset, usually appears between 50-60 years of age, and pathologically with Lewy bodies. *LRRK2* is the most frequently mutated gene in dominant PD (Lees et al, 2009).

Mutations in the glucocerebrosidase gene (*GBA*) are associated with Gaucher's disease, the most common lysosomal storage disorder. Parkinsonism is an established feature of Gaucher's disease and an increased frequency of mutations in *GBA* has been reported in several different ethnic series with sporadic PD. Heterozygous mutations in the *GBA* gene significantly increased (five times) the risk of PD (Sidransky et al, 2009). In addition, patients with heterozygous mutations in the *GBA* gene also have pathology similar to idiopathic PD, with the presence of Lewy bodies and α-synuclein aggregate. *GBA* mutations represent a significant risk factor for the development of PD and suggest that to date, this is the most common genetic factor identified for the disease (Neumann et al, 2009).

3.1 Autosomal dominant forms of Parkinson's disease

To date, there are two genes associated with dominant autosomal dominant PD: *SNCA*/α-synuclein (PARK1) and leucine rich repeat kinase 2 (*LRRK2*, PARK8).

3.1.1 *SNCA*/α-synuclein (PARK1)

SNCA located on chromosome 4q21 (PARK1) was the first gene associated with PD. First, mutations in this gene were identified in families of Greek and Italian origin in 1997 (Polymeropoulos et al, 1997). This discovery was very important, because the identification of mutations in this gene was the first evidence that PD could be due to a genetic cause. After the discovery of the first pathogenic mutation, p.Ala53Thr (Polymeropoulos et al, 1997), two mutations were identified in the *SNCA* gene: mutation in a German family p.Ala30Pro (Kruger et al, 1998) and p.Glu46Lys mutation in a Spanish family (Zarranz et al, 2004). Years later, in 2003, was discovered the first affecting the genomic triplication of *SNCA* locus in a large family with PD (known as the 'Iowa kindred') (Singleton et al, 2003). After identification of the *SNCA* triplication, duplication *SNCA* genomic locus have also been identified in familial and sporadic forms of PD (Chartier-Harlin et al, 2004).

The *SNCA* gene encodes a protein called α-synuclein. This protein consists of 140 amino acids and is highly expressed in the central nervous system. α-Synuclein is the major fibrillar component of the Lewy body (Spillantini et al, 1997). Although its function is still unknown, appears to be involved in synaptic plasticity, neuronal differentiation, and axonal transport and synaptic vesicles (Biskup et al, 2008).

Symptoms caused by mutations in the *SNCA* gene are variable, but usually comes with age at onset around 50 years and phenotypic characteristics common to Lewy body dementia, with deposits of α-synuclein fibril and / or protein Tau, where Lewy bodies are more distributed throughout the brain of what we usually see in the PD. Some patients have dementia, visual hallucinations, parkinsonism and fluctuating cognition and attention (for example, patients with the mutation p.Glu46Lys and *SNCA* locus triplication). In contrast, the families described with duplication of the *SNCA* locus appear to have a slower progression of the disease, age of onset is usually late and not have dementia (Hardy et al, 2009). These latter observations led to suggest that the evolution of the disease may be associated with a dose-related effect of the *SNCA* locus (Singleton et al, 2003).

3.1.2 *LRRK2*/Dardarin (PARK 8)

Another locus for a dominant form of PD was first mapped in a Japanese family on chromosome 12 and named PARK8 (Funayama et al, 2002). Missense mutations in the gene for *LRRK2* were found to be disease causing in 2004 (Paisan-Ruiz et al, 2004; Zimprich et al,

2004). The most common mutation is the p.Gly2019Ser, which also constitutes the most common mutation of both mendelian and sporadic PD (Healy et al, 2008). Although there are over 50 different mutations described in the gene for confirmation dardarin pathogenicity in some of these mutations are difficult (Paisán-Ruiz 2009).
LRRK2 contains 51 coding exons and encodes a protein of 2,257 amino acids called dardarin. Endogenous LRRK2 is ubiquitiously expressed within neurons and associates with membranes and lipid rafts. The protein is found in presynaptic terminals where it associates with vesicles and endosomes (Biskup et al, 2008). Its function remains unknown, although functional studies have found that certain mutants alter *LRRK2* kinase activity and this activity is crucial for the toxic effect of the protein. It has also been seen that certain *LRRK2* gene mutations cause neuronal death (Biskup et al, 2008). It is also believed that dardarin could be involved in vesicular traffic system (Shin et al, 2008).
Mutations in the *LRRK2* gene vary greatly depending on the patient's geographical origin. There is some ethnic influence in the changes associated with the gene *LRRK2*. p.Arg1628Pro and p.Gly2385Arg as mutations, which, being absent in the Caucasian population, significantly increase the risk of PD in Asian populations. Both mutations are present in the normal population with a frequency of 2.65% (p.Arg1628Pro) and 1.8% (p.Gly2385Arg), but its prevalence is significantly higher in patients with PD. In addition, the mutation p.Gly2019Ser, common in the Caucasian population, is rarely identified in the Asian population (<0.1%), however, two mutations adjacent to amino p.Gly2019, p.Ile2012Thr and p.Ile2020Thr, occur more frequently in Asians than in Caucasians (Paisán-Ruiz 2009).
The clinical presentation closely resembles sporadicPD, but patients tend to have a slightly more benign course and are less likely to develop dementia and a favorable response to treatment with levodopa. Unilateral tremor is usually the first symptom of the disease, progressing slowly and benign. Patients with mutations in the LRRK2 gene are prone to develop dystonia (Healy et al, 2008). The age of onset is very variable (from 28 to 90 years old), but with an average age approaching 60 years. A person who inherits the Gly2019Ser mutation has only 28% risk of developing parkinsonism when younger than 60 years of age, but the risk rises to 74% at 79 years of age (Paisán-Ruiz 2009). p.Gly2019Ser mutation carriers have been described with no parkinsonian symptoms, suggesting the existence of incomplete penetrance associated with this mutation, and homozygous carriers without additional clinical effect caused by gene dosage (Paisán-Ruiz 2009).

3.2 Autosomal recessive forms of Parkinson's disease

Loss-of-function mutations in four genes (*PRKN*, *DJ-1*, *PINK1*, and *ATP13A2*) cause early onset recessive parkinsonism (age of onset <40 years). Parkin mutations are the second most common genetic cause of L-dopa-responsive parkinsonism, whereas mutations in the other three genes are rare.

3.2.1 *PRKN*/parkin (PARK2)

The PARK2 locus was cloned by extensive linkage analysis conducted in 13 consanguineous families from Japan in 1997. Today, mutations (> 100 different mutations) in the *PRKN* gene are the most common genetic cause of early-onset parkinsonism (onset age <40 years). The clinical picture associated with mutations in this gene is also similar to idiopathic PD, with a slow disease progression and response generally appropiate to treatment with levodopa.

Patients often develop dyskinesias at low doses of levodopa and generally develop dystonia. Lewy bodies are usually not a common pathology (Khan et al, 2003).
Parkin protein localizes, although not predominantly, to the synapse and associates with membranes. In general parkin is a cytoplasmic protein and functions in the cellular ubiquitination/ protein degradation pathway as an ubiquitin ligase (Kubo et al, 2001).

3.2.2 *PINK1*/PTEN-induced putative kinase 1(PARK6)

Initially, the PARK6 locus was cloned in a large Sicilian family in 2001. Three years later, pathogenic mutations in a gene called *PINK1* were identified in several Italian families (Valente et al, 2004). Symptoms caused by this gene are very similar to that described in patients with mutations in the *PRKN* gene. However, the age of onset may be more variable, reaching present even at 68 years of age, but typically has a juvenile onset (Kumazawa et al, 2008).
PINK1 encodes a primarily mitochondrial protein kinase. Mutations in the PINK1-gene are much less common than parkin mutations, and probably account for only 1 to 4 % of early-onset cases (Valente et al, 2004; Kumazawa et al, 2008; Rogaeva et al, 2004).

3.2.3 *DJ-1* (PARK7)

Mutations in the *DJ-1* gene (PARK7) are another rare cause of recessive autosomal parkinsonism (Bonifati et al, 2003; Hedrich et al, 2004). The clinical picture with early-onset and slow progression is similar to other recessive autosomal forms of PD. The normal function of DJ-1 and its role in dopamine cell degeneration is unknown, but there is evidence linking DJ-1 to oxidative stress response and mitochondrial function (Hardy et al, 2009).

3.2.4 ATP13A2-5P-type ATPase (PARK9)

The locus PARK9, *ATP13A*2 was first identified in families of Chilean and Jordanian origin who had a syndrome known as Kufor-Rakeb. This disease is rare and presents with a rigid and akinetic parkinsonism and juvenile onset. Spasticity, Babinski signs, supranuclear gaze palsy and cognitive impairment are some of the clinical symptoms that often occur in this disease (Paisán-Ruiz et al, 2010). The gene encodes a protein lysosomal of 1,180 amino acids that are abundantly expressed in the brain and might act in the proteolytic degradation carried out in the lysosomes (Ramirez et al, 2006).

3.2.5 Other autosomal recessive forms of parkinsonism

Recently, mutations in the gene *PLA2G6* (phospholipaseA2 calcium-independent)(PARK 14) were also found present in individuals who had an akinetic and progressive parkinsonism. Cognitive impairment is a clinical symptom that often accompanies these patients. *PLA2G6* encodes a phospholipase enzyme of 752 amino acids. In general, the phospholipases induce changes in the composition of the membrane, activate the inflammatory cascade and alter cell signaling pathways of unknown function (Paisán-Ruiz et al, 2010).
Several familial cases with a complex parkinsonism and dystonia have been identified with mutations in the gene FBX07 (PARK15). The clinical features resembling parkinsonism caused by mutations in the *PRKN* gene. In fact, FBXO7 gene encodes a protein of 522 amino acids, which seems to be also involved in the system of ubiquitin-proteasome protein degradation (Di Fonzo et al, 2009; Paisán-Ruiz et al, 2010).

Recently, it has been shown that patients with mutations in the gene spatacsin (*SPG11*) (Non PARK locus) develop a juvenile parkinsonism similar to that caused by genes *ATP13A2*, *PLA2G6* and *FBX07*. These patients show a thinning of the corpus callosum, very characteristic signs of spastic paraplegia. The presenting symptoms of the disease are often both spasticity and parkinsonism (Paisán-Ruiz et al, 2010).

4. Clinical features

PD commonly presents with impairment of dexterity or, less commonly, with a slight dragging of one foot. The onset is gradual and the earliest symptoms might be unnoticed or misinterpreted for a long time. Fatigue and stiffness are common but non-specific complaints. Other initial symptoms are lugubrious stiff face, a hangdog appearance, a flexion of one arm with lack of swing, a monotonous quality to the speech, and an extreme slowing down. The early physical signs are often erroneously and a lag of 2 – 3 years from the first symptoms to diagnosis is not unusual. A change in a patient's writing can be present for several years before diagnosis, with a tendency to slope usually in an upward direction and for the writing to get progressively smaller and more cramped after a line or two (Lee et al, 2009).

Complaints within the first 2 years of the disease of falls (especially backwards), fainting, urinary incontinence, prominent speech, disturbed swallowing, amnesia, or delirium should raise the possibility of an alternative diagnosis.

In the late stages of PD, the face of patients is masked and expressionless, the speech is monotonous, festinant, and slightly slurred, and posture is flexed simian with a severe pill rolling tremor of the hands. Freezing of gait for several seconds can happen when attempting to enter the consulting room and, when starting to move again, the patient tends to move all in one piece with a rapid propulsive shuffle. These motor blocks lead to falls. All dextrous movements are done slowly and awkwardly, and assistance might be needed for dressing, feeding, bathing, getting out of chairs, and turning in bed. Constipation, chewing and swallowing difficulties, drooling of saliva, and urge incontinence of urine are common complaints.

Although PD has long been considered primarily a motor disorder Nonmotor symptoms (NMS) in PD are common and were recognized by James Parkinson himself. Thus, in his Essay on the Shaking Palsy in 1817, he referred to sleep disturbance, constipation, urinary incontinence and delirium (Parkinson, 1817). Numerous studies have now indicated that NMS is an integral symptom complex of PD, affecting memory, bladder and bowel, and sleep among others (Table 1) (Chaudhuri et al, 2006). It is commonly thought that NMS occur only in late or advanced PD but NMS can indeed present at any stage of the disease including early and pre-motor phase of PD. Several NMS of PD such as olfactory problems, constipation, depression and erectile dysfunction may predate the motor signs, symptoms and diagnosis of PD by a number of years (Chaudhuri et al, 2006; Tolosa et al, 2007).

Patients with PD are prone to have sleep disturbances that result in excessive daytime somnolence (EDS) and require proper identification and treatment (Comella, 2007). Sleep dysfunction in PD is usually manifest by difficulty in initiating sleep, fragmented sleep, REM behavior disorder (RBD), reversal of the sleep cycle, and EDS (Porter et al, 2008). It is possible that RBD might be early features of PD that antecede the onset of the classic motor features of the disease. In fact, in one study, RBD was found to have preceded the onset of PD symptoms in 52% of patients (Postuma et al, 2006). RBD in patients with PD is

frequently seen in association with visual hallucinations (Meral et al, 2007). The presence of RBD in patients with PD is also frequently associated with neuropsychiatric problems and cognitive impairment. Even the presence of RBD in a patient with PD without dementia predicts the subsequent development of cognitive impairment (Vendette et al, 2007).

Although, troublesome dysautonomia is recognized in advanced PD, cardiac (123)I-metaiodobenzylguanidine (MIBG) imaging demonstrates early cardiac sympathetic denervation in PD (low cardiac uptake) and not multiple system atrophy (MSA) where the heart is usually visualized (Goldstein et al, 2000). Cardiac sympathetic denervation has also been found in genetic forms of PD with alpha synuclein mutation (Singleton et al, 2004).

Neuropsychiatric problems such as dementia, delirium, anxiety, and depression occur at one time or another in most patients, and can potentially be more disabling than motor dysfunction.

Risk of dementia exists, particularly in those patients who present with prominent gait and speech disorders, depression, and a poor response to L-dopa. The greatest risk factor for dementia, however, is the age of the patient and not the duration of the disease (Levy, 2007). Visuospatial difficulties, disturbances of attention and vigilance, delirium, and executive dysfunction are more common in PD than in Alzheimer's disease (Noe et al, 2004). Visual hallucinations are commonly associated with PD dementia.

Depression is pervasive in PD and affects approximately 40% of patients at least once during the course of their disease (Starkstein et al, 1992). Studies have suggested that symptoms of depression may precede the development of PD.

5. Pharmacologic treatment

5.1 Neuroprotection

Several putative neuroprotective agents have been tested in placebo-controlled clinical trials. Some clinical trials had negative outcomes despite promising theoretical or preclinical evidence. These include the antioxidant vitamin E (Parkinson Study Group, 1993), the glutamate release inhibitor riluzole (Jankovic and Hunter, 2002) , coenzyme Q10 (Shults et al, 2002), glial cell line-derived neurotrophic factor (GDNF) (Nutt et al, 2003), the antiapoptotic agents TCH346 (Olanow et al, 2006), CEP-1437 (Parkinson Study Group, 2007), and the neuroimmunophilins (Gold and Nutt, 2002) which are thought to act via a possible trophic mechanism. Conversely, some putative neuroprotective agents have demonstrated significant benefits compared with controls, but still could not be unequivocally deemed to be neuroprotective because of the possibility of confounding symptomatic or pharmacologic effects. Although it is not possible to claim with certainty that any of these drugs are neuroprotective, many are routinely used by physicians based on the hope that they might slow disease progression. These agents are considered below.

5.1.1 Selegiline

Selegiline is a selective, irreversible inhibitor of monoamine oxidase-B (MAO-B). Selegiline was the first drug to be tested as a putative neuroprotective therapy in patients with PD based on its capacity to protect dopamine neurons by inhibiting the MAO-B oxidation of MPTP and blocking the formation of free radicals derived from the oxidative metabolism of dopamine (Olanow 1996). The initial advantages shown by selegiline have not been maintained. Furthermore, evidence is insufficient to make a conclusion on the neuroprotective, as opposed to the symptomatic effect of selegiline in PD (Parkinson Study Group, 1996).

Neuropsychiatric symptoms
Depression, apathy, anxiety
Anhedonia
Attention deficit
Hallucinations, illusion, delusions
Dementia
Obsessional and repetitive behaviour (usually drug induced)
Confusion
Delirium (could be drug induced)
Panic attacks
Sleep disorders
Restless legs and periodic limb movements
REM behaviour disorder and REM loss of atonia
Non-REM sleep related movement disorders
Excessive daytime somnolence
Vivid dreaming
Insomnia
Sleep disordered breathing
Autonomic symptoms
Bladder disturbances
Urgency
Nocturia
Frequency
Sweating
Orthostatic hypotension
Coat hanger pain
Sexual dysfunction
Hypersexuality (likely to be drug induced)
Erectile impotence
Dry eyes (xerostomia)
Gastrointestinal symptoms
Dribbling of saliva
Ageusia
Dysphagia/ choking
Reflux, vomiting
Nausea
Constipation
Unsatisfactory voiding of bowel
Fecal incontinence
Sensory symptoms
Pain
Paraesthesia
Olfactory disturbance
Other symptoms
Fatigue

Diplopia
Blurred vision
Seborrhoea
Weight loss
Weight gain (possibly drug induced)

Table 1. Nonmotor features of PD

5.1.2 Rasagiline

Rasagiline is another selective, irreversible MAO-B inhibitor. There are data from studies in vitro and in animal models have shown neuroprotective capacity by rasagiline (Sagi et al, 2007; Zhu et al, 2008).

To test for a possible neuroprotective effect in patients with PD, rasagilina had been shown to have a symptomatic effect in the TEMPO study (The Rasagiline Mesylate in Early Monotherapy for PD Outpatients) (Parkinson Study Group, 2002). ADAGIO (the Effect of Rasagiline Mesylate in Early PD patients) study was designed to verify these results. It demonstrated that early treatment with rasagiline 1 mg daily provided a benefit that was not obtained with the delayed introduction of the drug. These results are consistent with rasagiline having a possible neuroprotective effect (Olanow et al, 2009).

5.1.3 Dopamine agonist

Dopamine agonists have been studied for putative neuroprotective effects in PD, based on their capacity to protect dopamine neurons from a variety of toxins (Schapira, 2002). Indeed, the dopamine agonist pramipexole has been reported to protect dopamine neurons in MPTP-lesioned primates (Iravani et al, 2006).

Clinical trials have attempted to test the capacity of dopamine agonists to provide disease-modifying effects in PD. However, Class I randomized, controlled trials with bromocriptine (Olanow et al, 1995), pramipexol (Parkinson Study Group, 2000; Parkinson Study Group, 2002), and ropinirole (Rakshi et al, 2002; Whone et al, 2003) produced no convincing evidence of neuroprotection in early PD.

5.1.4 Levodopa

The only available placebo-controlled study of levodopa in relation to neuroprotection is inconclusive about any Neuroprotective, as opposed to symptomatic effect (Fahn et al, 2004). Mortality studies suggest improved survival with levodopa therapy (Rajput 2001).

5.2 Motor symptoms treatment of PD

5.2.1 Levodopa

Levodopa is the most effective drug for the symptomatic treatment of PD and the gold standard against which new therapies must be measured. Benefits are usually seen in all stages of the disease and can be particularly noteworthy in patients with early PD, in whom the drug can control virtually all of the classic motor features. Although prediction of the therapeutic response in an individual is not possible, motor symptoms initially improve by 20 – 70%. Speech, swallowing, and postural instability can improve initially, but axial symptoms are generally less responsive and seem to escape more readily from long-term control (Fahn et al, 2004).

Levodopa exerts its symptomatic benefits through conversion to dopamine, and is routinely administered in combination with a decarboxylase inhibitor (carbidopa, benserazide) to prevent its peripheral conversion to dopamine and the resultant nausea, vomiting and orthostatic hypotension. A combination of carbidopa/levodopa and the COMT inhibitor entacapone is available. There are also sustained-release formulations of levodopa although sustained-release formulations of levodopa are not as well absorbed as regular formulations, and doses 20% to 30% higher may be necessary to achieve the same clinical effect. A gel preparation of levodopa (Duodopa) has been used for intraintestinal infusion of the agent and is used in more advanced stages of disease.

Levodopa is absorbed in the small bowel by active transport through the large neutral amino acid (LNAA) pathway, and can be impaired by alterations in gastrointestinal motility and by dietary LNAAs, such as phenylalanine, leucine, and valine, which compete with levodopa for absorption through the LNAA (Nutt et al, 1984).

Acute side effects associated with levodopa include nausea, vomiting, and hypotension, but levodopa is generally well tolerated when it is gradually increased. Levodopa is generally started at a low dose to minimize these risks. Most people can be maintained over the first 5 years of the disease on 300 – 600 mg/day levodopa. Levodopa maintain a similar level of control in de novo PD after 5 years (Koller et al, 1999), and also in more advanced PD with a duration of about 10 years and without motor fluctuations(Goetz et al, 1988).

Chronic levodopa therapy is associated with motor complications, such as dyskinesias and motor fluctuations, in the majority of patients. Motor fluctuations include delayed onset of levodopa's therapeutic effect or its wearing off between doses. Dyskinesias are involuntary choreiform movements that can involve any part of the body and sometimes impose disabling or painful postures. A meta-analysis found 40% likelihood of motor fluctuations and dyskinesias after 4–6 years of levodopa therapy (Ahlskog and Muenter, 2001). Risk factors are younger age, longer disease duration, and levodopa (Denny AP and Behari M, 1999; Fahn et al, 2004). In individual studies, the percentage of fluctuations and dyskinesia may range from 10% to 60% of patients at 5 years on disease duration, and up to 80–90% in later years (Olanow et al, 2001). Patients with PD can also experience fluctuations in such nonmotor symptoms as mood, cognition, autonomic disturbances, pain, and sensory function (Witjas et al, 2002). Levodopa may also be associated with neuropsychiatric side effects, including cognitive impairment, confusion and psychosis. Importantly, many PD features are not satisfactorily controlled by, or do not respond to, levodopa. These include freezing episodes, postural instability with falling, autonomic dysfunction, mood disorders, pain and sensory disturbances, and dementia. Levodopa treatment can also be associated with a dopamine dysregulation syndrome in which patients compulsively take extra doses of levodopa in an addictive fashion. Although levodopa has been associated with impulse control disorders (ICDs) such as hypersexuality and pathologic gambling, these behaviors have primarily been reported to be associated with dopamine agonists (Ceravolo et al, 2010). In addition, chronic levodopa treatment has been associated with punding, which is a series of repetitive and purposeless behaviors, such as collecting or assembling and disassembling objects for no apparent reason (Evans et al, 2004).

There has long been a theoretical concern that levodopa might accelerate neuronal degeneration in PD because of the potential of the drug to generate free radicals through its oxidative metabolism (Olanow et al, 2004). However, most studies in animal models and humans do not show an accelerated loss of dopaminergic neurons to long-term levodopa therapy in usual clinical doses (Olanow et al, 2004). The Earlier vs Later Levodopa Therapy

in PD (ELLDOPA) study was the first double-blind, placebo-controlled trial to assess the safety and efficacy of different doses of levodopa and address the potential toxicity of levodopa in patients with PD (Fahn et al, 2004). The clinical results of this study certainly do not provide any evidence to suggest that levodopa is toxic or accelerates the development of disability in patients with PD and do not demonstrate any adverse effect of levodopa on PD progression.

5.2.2 Dopamine agonist

Dopamine agonists are a class of drugs with diverse physical and chemical properties. They share the capacity to directly stimulate dopamine receptors, presumably because they incorporate a dopamine-like moiety within their molecular configuration. Dopamine agonists have drawn particular interest as a treatment for PD because of their potential to provide antiparkinsonian effects with a reduction in the motor complications associated with levodopa. Today, dopamine agonists are also used as early symptomatic therapy to reduce the risk of developing the motor complications associated with levodopa therapy.

It is generally accepted that the shared D2-like receptor agonistic activity produces the symptomatic antiparkinsonian effect. This D2 effect also explains peripheral (gastrointestinal nausea and vomiting), cardiovascular (orthostatic hypotension) and neuropsychiatric (somnolence, psychosis, and hallucinations) side effects.

The first group of dopamine agonists used in the treatment of PD were ergot derivatives (bromocriptine, cabergoline, lisuride, pergolide, dihidroergocriptine). Numerous studies have demonstrated the effectiveness of these agents in PD as adjuncts to levodopa and shown that as monotherapy they are associated with a reduced risk of inducing dyskinesia compared with levodopa (Montastruc et al, 1994; Bracco et al, 2004; Oertel et al, 2006). However, their use has markedly declined due to the risk of valvular fibrosis and the introduction of nonergot dopamine agonists (apomorfine, pramipexole, ropinirole, rotigotine, piribedil). Although rare, cardiac dysfunction with valvular thickening and fibrosis has been reported with pergolide and cabergoline, presumably because they activate the 5HT2b receptor (Morgan and Sethi 2006; Zanettini et al, 2007; Roth BL 2007). In the nineties, nonergot dopamine agonists have largely supplanted the ergot agonists as the dopamine agonists of choice for the treatment of PD. Apomorphine is a short-acting dopamine agonist that is available in injectable form as a rescue drug for the management of "off" periods, and in some countries as an subcutaneous infusion therapy for the management of patients with advanced motor complications.

Levodopa is more efficacious than any orally active dopamine agonist monotherapy. The proportion of patients able to remain on agonist monotherapy falls progressively over time to <20% after 5 years of treatment. For this reason, after a few years of treatment, most patients who start on an agonist will receive levodopa as a replacement or adjunct treatment to keep control of motor parkinsonian signs. Over the last decade, a commonly tested strategy has been to start with an agonist and to add levodopa later if worsening of symptoms cannot be controlled with the agonist alone (Rinne et al, 1998; Parkinson Study Group 2000; Rascol et al, 2000).

From the limited data available (bromocriptine versus ropinirole, bromocriptine versus pergolide), the clinical relevance of the reported difference between agonists, if any, remains questionable (Mizuno Y et al, 1995; Korczyn et al, 1999).

Class I randomized, controlled trials demonstrate how early use of an agonist can reduce the incidence of motor complications versus levodopa (cabergoline (Bracco et al, 2004),

pramipexole (Parkinson Study Group, 2000), and ropinirole (Rascol et al, 2000; Whone et al 2003). Similar conclusions were reported with bromocriptine (Montastruc et al, 1994), and pergolide (Oertel et al, 2006) in several class II studies. There is no evidence to suggest that an agonist is more effective than another in preventing or delaying the time to onset of motor complications. Dopamine agonists serve to delay the onset of motor complications by delaying the time until levodopa is required, but do not prevent motor complications once levodopa is introduced. Indeed, two studies have now shown that the time to onset of motor complications from when levodopa is introduced is the same whether levodopa is used as initial therapy or as an adjunct to the dopamine agonist (Rascol et al, 2000; Constantinescu et al, 2007).

Regarding the treatment of non-motor symptoms in PD pramipexole has shown to have an antidepressant effect in several randomized, double-blind controlled studies (Corrigan et al, 2000; Lemke et al, 2006; Bxarone et al, 2010). A recent study with transdermal rotigotine 24 hours monotherapy vs placebo has shown an improvement in nocturnal sleep disturbance (assessed by the "Modified Parkinson's Disease Sleep Scale) and early-morning motor dysfunction (Trenkwalder et al, 2011).

There are long-acting preparation of pramipexole and ropinirole with 24-hour prolonged release. Also rotigotine by transdermal administration has been shown to have constant levels of drug with a single patch daily. This allows for less fluctuation in plasma drug levels and permits drug levels to be maintained during the waking day and to drop off during the night. This may lead to better compliance and more consistent symptom response throughout the day and perhaps better nighttime symptom control. In adjunct studies, ropinirole (Pahwa et al, 2007) and pramipexol (Hauser et al, 2010) 24 hours provided improvement in UPDRS motor and quality-of-life scores comparable with the immediate release form of the drug and was well tolerated.

Dopamine agonists and all other active dopamine-mimetic medications share a common safety profile. Accordingly, side effects such as nausea, vomiting, orthostatic hypotension, confusion and psychosis, may occur with administration of any of these agents. Hallucinations and somnolence are more frequent with some agonists than with levodopa and are particularly common in elderly people or patients with cognitive impairment (Etminan et al, 2001). The ergot-derived dopamine agonists can be associated with a Raynaud's-like phenomena, erythromelalgia, and pulmonary or retroperitoneal fibrosis (Andersohn and Garbe, 2009). These events are relatively uncommon and are not seen with the nonergot dopamine agonists. Valvular fibrosis may occur in as many as 30% of patients receiving ergot-based dopamine agonists and can lead to valvular dysfunction with the need for surgical repair in extreme cases. This has resulted in withdrawal of pergolide from the market, and a marked reduction in the use of the other ergot agonists (Zanettini et al, 2007; Roth 2007). When these agents are used, it is essential that patients be periodically monitored with echocardiography to detect valvular alterations.

Sedation with EDS and possible unwanted sleep episodes has been associated with the use of dopamine agonists. Dopaminergic medications and dopamine agonists in particular, are known to have dose-related sedative side effects (Frucht et al, 1999; Ferreira et al, 2000; Paus et al, 2003).

Other problems related to the use of dopamine agonists include weight gain (possibly related to overeating) (Nireberg and Waters, 2006), edema (especially in the lower extremities) (Kleiner-Fisman G and Fisman, 2007) and a variety of ICDs, such as pathologic

gambling, hypersexuality, and compulsive eating and shopping (Weintraub et al, 2006). Risk factors for ICDs include current use of dopamine agonists, particularly in high doses, young age of PD onset, and a premorbid or family history of ICDs or depression (Voon et al, 2006). ICDs were first identified in association with pramipexole, but have now been described with ropinirole and pergolide. Interestingly, they occur much less frequently with levodopa, although punding is primarily associated with chronic levodopa treatment. The precise mechanism whereby dopamine agonists might induce these ICDs is not known. It remains to be determined if dopamine agonists are directly responsible for inducing an ICD through a particular pattern of receptor stimulation, or if there is an underlying personality disorder that becomes clinically manifest with restoration of striatal dopaminergic tone.

5.2.3 Catechol-O-methyltransferase (COMT) inhibitors

Catechol-O-methyltransferase (COMT) inhibitors reduce the metabolism of levodopa, extending its plasma half-life and prolonging the action of each levodopa dose. Administration of levodopa with a COMT inhibitor increases its elimination half-life (from about 90 minutes to about 3 hours).

Two COMT inhibitors have been approved as adjuncts to levodopa for the treatment of PD; tolcapone and entacapone. Tolcapone inhibits COMT at peripheral level and to a lesser extent at the central level whereas entacapone acts only in the periphery.

COMT inhibitors are effective when administered in conjunction with levodopa and increase interdose, trough, and mean levodopa concentrations. Administration of levodopa plus a COMT inhibitor results in smoother plasma levodopa levels and more continuous brain availability compared with levodopa alone (Muller et al, 2006). Thus, administering levodopa with a COMT inhibitor has the potential to deliver levodopa to the brain in a more predictable and stable fashion, thus decreasing the fluctuations in levodopa concentrations seen when standard levodopa is administered intermittently.

Double-blind, placebo-controlled trials have demonstrated that both tolcapone and entacapone increase "on" time, decrease "off" time, and improve motor scores for patients with PD who experience motor fluctuations. Moreover, this benefit was associated with a reduction in the mean daily dose of levodopa (Kurth et al, 1997; Parkinson Study Group, 1997). Benefits have been shown to persist for 3 years or longer (Larsen et al, 2003). In general, superior clinical benefits have been achieved with tolcapone, reflecting the increased level of COMT inhibition.

Benefits with COMT inhibitors have also been observed in stable patients PD who have not yet begun to experience motor fluctuations (Waters et al, 1997; Olanow et al, 2004).

There has also been interest in the potential of COMT inhibitors to reduce the risk for motor complications associated with standard doses of levodopa (Olanow and Stocchi, 2004). This is based on the concept that intermittent doses of short-acting levodopa leads to pulsatile stimulation of dopamine receptors and motor complications. COMT inhibitors extend the elimination half-life of levodopa and thus, if administered frequently enough, might provide continuous levodopa to the brain. Although studies in monkeys showed that administration of levodopa plus the COMT inhibitor entacapone reduced dyskinesias compared with treatment with levodopa alone (Smith et al, 2005), these results have not been observed in patients. Specifically, in a recent clinical trial, Stalevo Reduction in Dyskinesia Evaluation (STRIDE-PD), which compared the time to onset and frequency of dyskinesia in levodopa-naïve PD patients who were randomized to initiate levodopa

therapy with carbidopa/levodopa compared with carbidopa/levodopa/entacapone (Stalevo), was demonstrated that patients randomized to Stalevo had an increased frequency and a shorter time to dyskinesia than did those on standard levodopa (Stocchi et al, 2010).
COMT inhibitors increase levodopa bioavailability, and hence they increase the incidence of dopaminergic adverse reactions, including nausea, and cardiovascular and neuropsychiatric complications. Diarrhoea and urine discoloration are the most frequently reported non-dopaminergic adverse reactions. Tolcapone can elevate liver transaminases, and fatal cases of liver injury are reported (Assal et al, 1998). Currently, the drug has been reintroduced to the market in many countries, but has been imposed strict safety restrictions.

5.2.4 MAO-B inhibitors

Selegiline and rasagiline inhibit the action MAO-B. MAO-B prevents the breakdown of dopamine, leading to greater dopamine availability. Mechanisms besides MAO-B inhibition may also contribute to the clinical effects (Olanow, 1996). Unlike selegiline, rasagiline is not metabolized to amphetamine, and has no sympathomimetic activity.
Selegiline was initially approved as an adjunct to levodopa in patients with motor fluctuations. However, selegiline is primarily used in early disease, based on its putative neuroprotective effects (see section on Neuroprotection) and its capacity to provide mild symptomatic benefits (Parkinson Study Group 1993). When combined with levodopa, it can enhance dopaminergic side effects and lead to increased dyskinesia and neuropsychiatric problems, particularly in the elderly.
Rasagiline has been approved for use in patients with both early and advanced PD. Rasagiline is an irreversible inhibitor of MAO-B. It is more potent and more selective than selegiline, and does not generate amphetamine or methamphetamine metabolites. TEMPO study, a class I study with rasagiline, showed improvement of both the total UPDRS and the motor subscale of the UPDRS in patients treated with rasagiline versus placebo (Parkinson Study Group 2002). Recently published data on long-term efficacy of rasagiline in patients who participated in the TEMPO study, showing maintenance of rasagiline as monotherapy in about half of patients after two years of follow-up (Lew et al, 2010). In ADAGIO study early vs delayed start rasagiline 1 or 2 mg/day were compared. The results of this study suggest that early treatment with rasagiline 1 mg/ day provides benefits that cannot be attained with later initiation of the drug, and argues for starting symptomatic treatment at an earlier time point than has conventionally been used (Olanow et al, 2009). The PRESTO (Parkinson Study Group, 2005) and LARGO (Rascol et al, 2005) study have demonstrated the benefit of rasagiline in patients with motor fluctuationes.
Safinamide is a new MAO-B inhibitor that is currently being studied as a treatment for early and advanced PD. In addition to its MAO-B inhibitor properties, it also inhibits dopamine uptake, and blocks sodium channels and glutamate release. A randomized, placebo-controlled trial of safinamide in early to midstage PD demonstrated modest antiparkinsonian effects, with benefits specifically noted in patients who were already receiving a dopamine agonist (Stocchi et al, 2004).
MAO inhibitors are generally well tolerated. Amphetamine metabolites of selegiline may induce insomnia. At the daily doses currently recommended, the risk of tyramine-induced hypertension (the cheese effect) is low. Also this reaction has not been reported with

selective inhibitors of MAO-B (Heinonen EH and Myllylä, 1998). Concerns that the selegiline/levodopa combination increased mortality rates (Ben-Shlomo et al, 1998) have been allayed (Olanow et al, 1998). MAO inhibitors may also interfere with serotonin metabolism and induce a serotoninergic syndrome, although this reaction is rarely presented (Ritter and Alexander, 1997).

5.2.5 Other antiparkinsonian drugs

5.2.5.1 Anticholinergics

The precise mechanism of action of anticholinergic drugs in PD is not known although are believed to act by correcting the disequilibrium between striatal dopamine and acetyl choline activity. Some anticholinergics, e.g. benzotropine, can also block dopamine uptake in central dopaminergic neurons. The anticholinergics used to treat PD specifically block muscarinic receptors.

The use of anticholinergics has dramatically declined in the era of levodopa and dopamine agonists, but these agents are still occasionally used. Anticholinergic drugs are typically used in younger patients with PD in whom resting tremor is the dominant clinical feature and where cognitive function is preserved. Anticholinergic drugs are of little value in the treatment of other parkinsonian features such as rigidity, akinesia, gait dysfunction, or impaired postural reflexes (Cantello et al, 1986). Currently trihexyphenidyl is the most widely used of the anticholinergic drugs.

The most commonly reported side effects are blurred vision, urinary retention, nausea, constipation (rarely leading to paralytic ileus), and dry mouth. The incidence of reduced sweating, particularly in those patients on neuroleptics, can lead to fatal heat stroke. Anticholinergics are contraindicated in patients with narrow-angle glaucoma, tachycardia, hypertrophy of the prostate, gastrointestinal obstruction, and megacolon. Impaired mental function (mainly immediate memory and memory acquisition) is a well-documented central side effect that resolves after drug withdrawal. Therefore, if dementia is present, the use of anticholinergics is contraindicated (Van Herwaardenet al, 1993).

5.2.5.2 Amantadine

Amantadine's mechanism of action remains unclear. A blockade of N-methyl-D-aspartate (NMDA) glutamate receptors and an anticholinergic effect are proposed, whereas other evidence suggests an amphetamine-like action to release presynaptic dopamine stores (Kornhuber et al, 1994).

Amantadine has been shown to improve akinesia, rigidity, and tremor in placebo-controlled trials when used as monotherapy or in combination with levodopa. Early studies suggested that benefit with amantadine is transient, but some patients enjoy more sustained benefits (Butzer et al, 1975; Timberlake and Vance, 1978).

Amantadine is the only currently available agent that is capable of blocking dyskinesia without interfering with the parkinsonian response and has proven to be of considerable benefit for some patients. The utilization of amantadine, however, may be limited by its propensity to cause cognitive impairment, particularly in patients with advanced PD (Verhagen Metman et al, 1998; Metman et al, 1999).

Side effects include confusion, hallucinations, insomnia, and nightmares. These are more common in older patients, but can be seen in patients of any age. Peripheral side effects include livedo reticularis and ankle edema, although these are rarely severe enough to limit

treatment. Dry mouth and blurred vision can occur and are presumed related to its peripheral anticholinergic effects.

5.3 Nonmotor symptoms treatment of Parkinson's disease (Table 2)

NMS in PD include neuropsychiatric symptoms, sleep disturbances, autonomic dysfunction, and pain or sensory problems. Such symptoms are a frequent accompaniment to the motor disability with continuing disease progression (Chaudhuri et al, 2006). Although several nondopaminergic systems within the brainstem and cortex are involved in PD, specific clinicopathological correlation for such features remains uncertain, and despite the increasing recognition of these problems, specific pharmacological therapies that target the relevant nondopaminergic neurotransmitter system are limited.

The management of dementia in PD is a pressing problem because cognitive impairment is a common and important source of disability. As dementia in PD is associated with a cholinergic deficit, trials of the cholinesterase inhibitors donepezil and rivastigmine have been carried out in patients with dementia. In these studies, both rivastigmine (Emre et al, 2004) and donepezil (Ravina et al, 2005) showed a modest but significant improvement compared with controls without worsening of parkinsonism.

The cause of psychotic symptoms in PD is probably multifactorial, involving interplay between pathological processes and dopaminergic medications. The management of hallucinations and delirium in the patient with PD must begin with a pretreatment setting eliminating those drugs that can cause hallucinations or delusions and adjusting the dose of levodopa. When the adjustments fail to eliminate or sufficiently alleviate hallucinations and/or cannot be accomplished without inducing a meaningful deterioration in PD features, neuroleptic therapy should be considered. Haloperidol, perphenazine, or chlorpromazine are effective antipsychotics, but are not recommended for patients with PD because of their capacity to block striatal dopamine D2 receptors and exacerbate parkinsonian features. The "atypical" neuroleptics are the preferred agents to use (especially clozapine (Parkinson Study Group, 1999) and quetiapine (Fernandez et al, 2003)), and can often effectively treat hallucinations and psychosis induced by dopaminergic medications. They are called "atypical" because among other factors they preferentially block limbic and cortical dopamine receptors, but are relatively devoid of D1 and D2 receptor-blocking properties (Friedman and Factor, 2000).

Anxiety and depression are extremely common in PD and frequently coexist. Both might respond to dopaminergic therapies, and anxiety in particular can be experienced when the motor effects of levodopa have worn off (ie, during an "off period). However, successful management of these mood disorders often requires treatments in addition to dopaminergic agents, which suggests that non-dopaminergic neurotransmitters are involved. The current management of depression and anxiety in PD involves the use of conventional treatments that enhance serotonergic neurotransmission, such as selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants. Although in clinical practice many patients with PD do experience a significant improvement in mood symptoms with these agents (whatever the exact mechanism of action), the true effectiveness in PD has not been established owing to the limited numbers of available randomised controlled trials (Weintraub et al, 2005; Chung et al, 2003). Some antidepressants, which are undergoing investigation for depression and anxiety in PD, are also selective noradrenergic reuptake inhibitors (eg, duloxetine, venlafaxine, and desipramine).

Patients with PD can experience various behavioural problems as a consequence of dopaminergic medications, including impulse control disorders, such as pathological gambling, shopping, eating, and hypersexuality,(Voon et al, 2011) and abnormal excessive motor behaviours ranging from purposeless fiddling to complex stereotypic activities, known as "punding" (Evans et al, 2004). These problems have been particularly associated with dopamine agonists, but also with levodopa. The precise mechanism whereby dopamine agonists might induce these ICDs is not known. Treatment of each patient should be individualized based on the magnitude of the ICD problem and the need for dopaminergic drugs to control PD features. The symptoms might resolve on reducing or discontinuing the dopamine agonists, although they can persist in some patients (Mamikonyan et al, 2008). Other approaches could include trials of various psychoactive agents and psychosocial interventions and referring patients for appropriate counseling services.

Sleep dysfunction in PD is usually manifest by difficulty in initiating sleep, fragmented sleep, reversal of the sleep cycle, and EDS. Sleep disturbances in PD are multifactorial and may be related to aging, parkinsonian motor dysfunction, dyskinesia, pain, nocturia, nightmares, dopaminergic and nondopaminergic medications, cognitive impairment, and a variety of specific sleep disorders, including restless legs syndrome (RLS), periodic limb movements of sleep (PLMS), RBD, and sleep apnea. Collectively, they contribute to the increase in daytime sleepiness that is so frequently found in patients with PD (Tandberg et al, 1999; Comella, 2007). Dopaminergic medications and particularly dopamine agonists can have a complex effect on sleep. Sometimes these medications cause insomnia or sleepiness. In other situations they may improve nocturnal immobility, and in this way improve the quality of sleep (Montastruc et al, 2001; Brodsky et al, 2003). Thus, dopaminergic medications can either improve or worsen sleep in patients with PD. RBD in patients with PD may be effectively treated with low-dose clonazepam (0.25 to 1.0 mg nightly). The wake-promoting drug modafinil, which possibly affects histamine release in the hypothalamus, is currently used as an option to treat excessive daytime sleepiness in patients with PD (Morgenthaler et al, 2007). Is currently being assessed two other drugs (the BF 2.649 a selective histamine H3 inverse agonist and the caffeine, a non-selective adenosine antagonist) in the treatment of EDS in PD patients.

Drugs currently used to treat orthostatic hypotension in PD include midodrine, a sympathomimetic, and fludrocortisone, a mineralocorticoid. Supine hypertension is a potential side-effect of both of these approaches. The acetylcholinesterase inhibitor pyridostigmine bromide has been suggested to reduce orthostatic hypotension with less effect on supine hypertension, although evidence is limited (Low and Singer, 2008). L-threo-3, 4- dihydroxyphenylserine is a synthetic amino acid precursor of noradrenaline that is available for freezing of gait in PD and orthostatic hypotension in autonomic failure (Mathias et al, 2001). However, few randomised controlled trials few randomised controlled trials (RCTs) of treatment for orthostatic hypotension have been undertaken specifically in PD, but rather have involved mixed populations of patients including multiple system atrophy, in which the pathophysiology of orthostatic hypotension is different. Thus, the true efficacy of treatments for orthostatic hypotension in PD remains unclear.

Urinary symptoms can be troublesome in advanced PD. Current treatments are drugs for overactive bladder symptoms, such as the muscarinic antagonists oxybutynin and tolterodine. However, such drugs are typically poorly tolerated in patients with advanced PD due to central and peripheral anticholinergic side-effects. Another muscarinic

antagonist, trospium chloride, has potentially fewer central side-effects due to poor penetration of the blood – brain barrier, and is effective for treating overactive bladder symptoms (Staskin, 2006).

Postural instability is a late complication of PD which can lead to a mounting fear of falls with increasing immobilisation and dependency. Most falls in patients with PD occur in a forward or sideways direction and are due to turning difficulties, gait and postural asymmetries, problems with sensorimotor integration, difficulties with multitasking, failure of compensatory stepping, and orthostatic myoclonus (Bloem et al, 2004). Skilled physical therapy with cueing to improve gait, cognitive therapy to improve transfers, exercises to improve balance, and training to build up muscle power and increase joint mobility, is efficacious (Keus et al, 2007). Regular physical and mental exercise should be encouraged at all stages of the disease. Benzodiazepines should be avoided wherever possible because they increase the risk of falling.

Insomnia
Adjust dopaminergic drugs, sleep hygiene techniques or clonazepam
Depression
Serotonin and noradrenergic reuptake inhibitors or tricyclic antidepressants
Rapid eye movement behaviour disorders
Adjust Parkinson's disease drugs or clonazepam
Fatigue
Amantidine or selegiline
Day time sleepiness
Modafinil
Psychosis and hallucinations
Adjust Parkinson's disease drugs or antipsychotic (clozapine, quetiapine)
Constipation
Osmotic laxatives (macrogol)
Urinary urgency
Check drugs, anticholinergic bladder stabilisers, and desmopressin for nocturia
Impotence
Sildenafil, tadalafil, and vardenafil
Pain
Adjust Parkinson's disease drugs and muscle relaxants
Restless legs
Dopamine agonists
Orthostatic hypotension
Adjust Parkinson's disease drugs; increase water and salt intake; fludrocortisone, ephedrine, or midodrine
Drooling
0-5% atropine eye drops sublingually, scopoderm patch, or botulinum toxin injections into salivary glands
Excessive sweating
Adjust Parkinson's disease drugs, propantheline, propranolol, or topical aluminium creams

Table 2. Treatment of Non motor symptoms of PD

6. Surgical procedure for the treatment of Parkinson's disease

The capacity of surgical therapies to provide benefit for patients with PD who can no longer be satisfactorily controlled with medical therapies due to motor complications has been a major advance in the modern treatment of PD (Hallett and Litvan, 2000). Surgical therapies have historically used ablative procedures (e.g., chemical, radiofrequency, or thermal lesions) to make a destructive lesion in overactive or abnormally firing brain targets. However, ablative procedures are associated with the risk of inducing damage to neighboring structures with consequent neurologic dysfunction. The introduction in 1987 of high-frequency deep brain stimulation (DBS) procedures in PD has resolved many of these issues. High frequency stimulation of specific brain targets induces functional benefits that simulate the effects of a destructive lesion, but without the need for making a destructive brain lesion. DBS is performed by implanting an electrode with four contacts into a target site within the brain and connecting it to a pulse generator placed subcutaneously over the chest or abdomen wall. Stimulator settings can be adjusted periodically with respect to electrode configuration, voltage, frequency, and pulse width (Bergman et al, 1990; Olanow et al, 2000).

The mechanism of action of high-frequency DBS is still not clear, even more than 21 years after its introduction. The mechanism is believed to be independent of the target, because DBS mimics the effects of ablation in all targets used to date, but its effects depend on stimulation rather than on the creation of a lesion.

Patients who are thought to benefit from DBS are those affected by clinically diagnosed idiopathic PD, in whom the cardinal symptoms of the disease— bradykinesia, rigidity, and tremor— are likely to be significantly improved (Krack et al, 2003; Deuschl et al, 2006). Those who show improvement with the optimum adjustment of anti-PD drugs or suprathreshold levodopa dose (300 mg per dose) are highly likely to show a similar improvement after optimum placement of the electrodes (Charles et al, 2002). Higher baseline scores on section III (motor) of the unified PD rating scale (UPDRS) and higher baseline levodopa responsiveness are independent predictors of greater change in motor score after surgery. Midline symptoms, dysautonomic symptoms, and gait disturbance unresponsive to levodopa (ie, freezing) are only slightly improved, if at all (Xie et al, 2001).

The different surgical targets exist in the treatment of PDare as follows: - Ventral intermediate (VIM) nucleus of the thalamus: stimulation procedures in this target provide potent antitremor (Narabayashi, 1989) and antidyskinesia (Narabayashi et al, 1984) effect in PD. However, the thalamus is rarely selected as a target site today because similar benefits can be obtained with other targets that are associated with more widespread antiparkinsonian effects. Subthalamic nucleus (STN) or internal segment of the globus pallidus (GPi)—physiologic and metabolic studies indicate that neurons in both the STN and GPi are overactive in PD (Crossman et al, 1985; Mitchell et al, 1989), and that lesions of these structures provide antiparkinsonian benefits in animal models of PD (Bergman et al, 1990; Brotchie et al, 1991; Guridi et al, 1994;). Both ablation and high frequency stimulation of these targets have been shown to provide antiparkinsonian benefits as well as a profound reduction in dyskinesia (especially GPi) in patients with PD. Although the STN is currently the preferred surgical target in most centers, there is no conclusive data indicating that comparable results cannot be obtained with stimulation of the GPi (Follet et al, 2010). Patients undergoing subthalamic stimulation required a lower dose of dopaminergic agents

than did those undergoing pallidal stimulation.- Pedunculopontine nucleus (PPN)—the PPN is a diffuse nucleus that extends throughout the upper brainstem. Stimulation and lesions in the PPN influence locomotion, and for this reason it has been referred to as the mesencephalic locomotor center (Pahapill and Lozano, 2000). Preliminary studies suggest that stimulation of the PPN may provide locomotor benefits for patients with PD (Stefani et al, 2007). DBS of the PPN is being actively investigated.

Side effects of DBS can be related to the surgical procedure, the device, or to the stimulation. There is a risk of hemorrhage and damage to neighboring brain structures, although risks are less than are seen with ablative procedures, particularly when performed bilaterally (Hallett and Litvan, 2000). Complications associated with the device can be related to infection or mechanical problems (e.g., lead fracture, movement of the electrode, skin erosion), and may require lead removal or reimplantation. Side effects related to stimulation are generally transient and may be controlled by adjusting the stimulation variables. The battery must be periodically replaced.

7. Recommendations for the management of Parkinson's disease

The optimal time frame for onset of therapy has not been clearly defined. Once parkinsonian signs start to have an impact on the patient's life, initiation of treatment is recommended. For each patient, the choice between the numerous effective drugs available is based in several factors. These factors include considerations related to the drug (efficacy for symptomatic control of parkinsonism/prevention of motor complications, safety, practicality, costs, etc.), and the patient (symptoms, age, needs, expectations, experience, co-morbidity, socioeconomic level, etc.).

Currently, there is no uniform proposal on initiating symptomatic medication for PD. In the past, levodopa was traditionally used to initiate therapy for PD because it was the most effective symptomatic agent, and levodopa is still commonly used as initial therapy by some physicians. Today, many movement disorder neurologists have elected to initiate symptomatic therapy with a dopamine agonist in appropriate patients, and to supplement with levodopa when satisfactory control cannot be attained with dopamine agonist monotherapy. This treatment philosophy is based on the body of laboratory and clinical information indicating that dopamine agonists are associated with a reduced risk of inducing motor complications compared with levodopa. Dopamine agonist use as as initial therapy because they delay the time until levodopa is required and permit use of lower doses of levodopa. To begin with levodopa is the preferred treatment for patients with PD with cognitive impairment, the elderly who have a reduced propensity to develop motor complications, and patients suspected of having an atypical parkinsonism who are undergoing a trial of dopaminergic therapy.

MAO-B inhibitors such as selegiline and rasagiline provide another therapeutic option in early disease. MAO-B inhibitors have been shown to provide modest antiparkinsonian effects when used as monotherapy and also delay the need for levodopa. The symptomatic effect is more modest than that of levodopa and (probably) dopamine agonists, but they are easy to administer (one dose, once daily, no titration). Furthermore the TEMPO and the ADAGIO studies suggest that early treatment with rasagiline provides benefits that cannot be attained with later introduction of the same medication (Parkinson Study Group, 2002;

Olanow et al, 2009). Although this does not establish neuroprotection and long-term studies are required to determine the effect of the drug on cumulative disability in the long run, it does indicate that earlier treatment with rasagiline may provide a better outcome, at least at the 18-month time point. For these reasons, many physicians now choose to initiate therapy in patients with early PD with an MAO-B inhibitor.

There may be advantages to initiating therapy in patients with early PD with both an MAO-B inhibitor and a dopamine agonist (not at the same time) to enhance clinical benefits and further delay the need for levodopa. However, there have been no studies as yet examining the effects of combining an MAO-B inhibitor with a dopamine agonist on the need for levodopa and the risk of inducing dyskinesia. However, subset analyses in studies testing rasagiline in advanced patients (Parkinson Study Group, 2005; Rascol et al, 2005) and preliminary studies with a new MAO-B inhibitor safinamide, (Stocchi et al, 2004) suggest that adding an MAO-B inhibitor to a dopamine agonist improves UPDRS scores.

Amantadine or anticholinergics are not routinely prescribed in patients with early PD, although some movement disorder specialists might use anticholinergics if tremor is the predominant feature in young patient with PD.

There are a variety of ways to enhance motor response in patients who experience suboptimal motor control with dopamine agonist or levodopa monotherapy. The simplest approach is to gradually raise the dose of the dopaminergic agent. However, high doses of dopamine agonists can be associated with neuropsychiatric side effects, sedation and ICDs. If patients cannot be satisfactorily controlled on an agonist, then levodopa should be added. If the patient is receiving levodopa monotherapy, increased doses might be effective. Higher doses are associated with an increased risk of motor complications, but may be justified if required to provide a satisfactory clinical response. The addition of a dopamine agonist may enhance benefit without increasing the risk of motor complications. COMT and/or MAO-B inhibitors may also be useful in managing patients with a suboptimal clinical response. The use of a subcutaneous apomorphine penject as a rescue device for unpredictable refractory off periods can also be helpful in some instances, and its fast action helps to restore confidence in patients becoming insecure about leaving home (Ostergaard et al, 1995).

Despite adjustments of the timing and dose frequency of levodopa, motor fluctuations and dyskinesias can mark the long-term therapeutic benefit. Amantadine is an effective anti-dyskinetic agent in some patients. Subcutaneous waking day apomorphine pump is a highly effective treatment for refractory motor fluctuations. Orally administered anti-parkinsonian medication should be adjusted obtain thebest results for dyskinesia reduction and off periods. Enteric administration of a soluble formulation of levodopa (Duodopa) through gastro-jejunostomy is another highly effective medical option for patients who failed to, or are reluctant to, try the apomorphine pump. Infusion therapies is based on the principle that continuous infusion of a dopaminergic agent provides more constant and physiologic activation of striatal dopamine receptors than is accomplished with intermittent administration of the same drug, and thereby reduces the risk of motor complications. Continuous infusion of either levodopa or apomorphine has been tested in patients with advanced PD and consistently been reported to reduce the frequency of motor complications (Manson et al, 2002; Antonini et al, 2007). Sustained improvement in motor performance with a great reduction in drug-induced involuntary movements can also be achieved by functional neurosurgery with bilateral deep brain stimulation of the STN or GPi.

8. Experimental approaches

Cell-based therapies have been studied based on the notion that transplantation of dopaminergic cells could replace dopamine neurons, which degenerate in PD, and restore dopaminergic function in a more physiologic manner than can be achieved with oral therapies (Lindvall and Bjo¨rklund, 2004). Fetal nigral transplantation has been the best studied of these approaches to date. Numerous laboratory studies have demonstrated that embryonic dopaminergic neurons implanted into the denervated striatum can survive, extend axons, provide organotypic innervations of the striatum, produce dopamine, and provide behavioral benefits in the 6-OHDA rodent and MPTP-monkey (Olanow et al, 1996). These studies have served as the basis for initiating clinical trials in patients with PD. To date, there is no universal agreement on the optimal transplant protocol. Open-label clinical trials using a variety of different transplant regimens produced variable clinical results. Various types of cells have been used (adrenal gland, mesencephalic fetal grafts, and more recently, epithelial retinal cells). Stem cells are also being investigated, which might be better tolerated immunologically, but raise their own (oncological) problems. Despite the elegance of this approach, it is still experimental and is not currently available to patients (Morizane et al, 2008). Intrastriatal carotid body (CB) transplants have been assayed in animal models of PD to test whether they increase the striatal dopamine levels and/or exert a neuroprotective action on the nigrostriatal pathway. Currently it being studied the in vitro formation of new CB tissue derived from adult CB stem cells, given the limitations of previous studies have been presented with autotransplantation of CB in patients with PD (López-Barneo et al, 2009).

Gene delivery approaches are also being actively investigated as a possible treatment for PD. In this technology, viruses are used as vectors to introduce the DNA of a desired protein into the genome of cells within a specific brain target. Furthermore, promoters can ensure that the virus vector infects specific brain cells (e.g., TH promoter targets dopamine cells). This sequence can thus potentially result in continuous production of the desired therapeutic protein in the desired target region of the brain (Dass et al, 2006). Most human studies have used the adeno-associated virus serotype 2 (AAV-2) as the vector, as AAV-2 does not induce an immune response and permits long-term expression of the transgene. No clinically significant or unanticipated adverse events have been encountered in any of the gene therapy studies performed to date (Svendsen, 2007). Different gene therapy approaches are currently being tested in PD, e.g trophic factors such as glial-derived nerve factor (Lang et al, 2006) or neurturin (Marks et al, 2010).

9. Conclusions

The current knowledge of the disease continues to evolve and be challenged by scientific discovery. Further research on the function of the proteins identified by the susceptibility genes, the interplay of the disease process with normal ageing, and the nature of environmental triggers that unmask the disease process will be needed if we are to develop reliable biomarkers and a cure for this disabling movement disorder. Although it is producing significant progress in new therapeutic options important unmet medical needs remain, and even more effective therapeutic interventions are required for the successful management of the patient with PD. Many such agents are now in development. However, future strategies need to focus on more selective targeting of subtypes of neurotransmitter

receptors to reduce side effects and optimise benefit. Finally, the development of neuroprotective agents in PD has to date focused on preventing dopamine cell loss. However, to be optimally effective, such therapies will also need to target nondopamine cells involved in the multisystem disease process.

10. References

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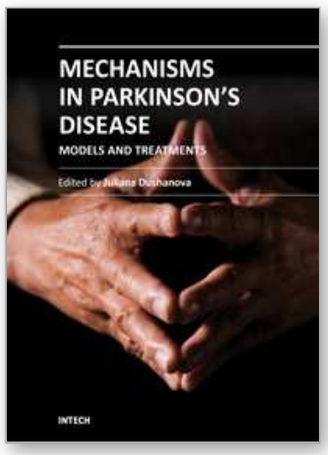

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Parkinson's disease (PD) results primarily from the death of dopaminergic neurons in the substantia nigra. Current PD medications treat symptoms; none halt or retard dopaminergic neuron degeneration. The main obstacle to developing neuroprotective therapies is a limited understanding of the key molecular mechanisms that provoke neurodegeneration. The discovery of PD genes has led to the hypothesis that misfolding of proteins and dysfunction of the ubiquitin-proteasome pathway are pivotal to PD pathogenesis. Previously implicated culprits in PD neurodegeneration, mitochondrial dysfunction, and oxidative stress may also act in part by causing the accumulation of misfolded proteins, in addition to producing other deleterious events in dopaminergic neurons. Neurotoxin-based models have been important in elucidating the molecular cascade of cell death in dopaminergic neurons. PD models based on the manipulation of PD genes should prove valuable in elucidating important aspects of the disease, such as selective vulnerability of substantia nigra dopaminergic neurons to the degenerative process.

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
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