



## Parkinson's Disease: *Old Concepts and New Challenges*

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It is highly unlikely that James Parkinson (1755-1824), who first described the “paralysis agitans” in his “Assay on the Shaking Palsy” in 1817 (years later rebadged by Jean-Martin Charcot as Parkinson’s disease), could have imagined that the disorder that today bears his name would become the neurodegenerative disorder that, after Alzheimer’s disease, has the largest impact on the elderly population. With a prevalence ranging from 35.8 per 100,000 to 12,500 per 100,000 and annual incidence estimates ranging from 1.5 per 100,000 to 346 per 100,000 in different countries [1-3], Parkinson’s disease is a major age-related health problem [4,5]. Meta-analysis of the worldwide data indicates a rising prevalence of Parkinson’s disease with age (41 per 100,000 at 40-49 years; 107 at 50-59 years; 173 at 55-64 years; 428 at 60-69 years; 425 at 65-74 years; 1,087 at 70-79 years; and 1,903 per 100,000 at over age 80), that has a characteristic distribution by geographic location (a prevalence of 1,601 per 100,000 in patients from North America, Europe and Australia, and a prevalence of 646 per 100,000 in Asian patients) [6]. Parkinson’s disease is more prevalent in males (1,729 per 100,000, > 65 yrs) than in females (1,644 per 100,000), with a peak prevalence in the age group of  $\geq 90$  years (4,633 cases per 100,000), and a mean prevalence of 1,680 per 100,000 in people older than 65 years of age [7]. Prevalence and incidence Male/Female ratios increase by 0.05 and 0.14, respectively, per 10 years of age. Incidence is similar in men and women under 50 years (M/F ratio < 1.2), and over 1.6 times higher in men than women above 80 years [8]. Furthermore, PD coexists with dementia in over 25% of the cases and with depression in over 30% of the cases in some countries [7].

Associated with different potentially pathogenic risk factors (toxins, drugs, pesticides, brain micro trauma, focal cerebrovascular damage, genomic defects), Parkinson’s disease neuropathology is characterized by a selective loss of dopaminergic neurons in the substantia nigra pars compacta, with widespread involvement of other brain structures and peripheral tissues [9].

Parkinson’s disease-related neurodegeneration is likely to occur several decades before the onset of the motor symptoms (rigidity, bradykinesia, resting tremor, postural instability) [9]. As in other prevalent age-related neurodegenerative disorders, it is plausible that the confluence of genomic vulnerability with diverse environmental factors may be responsible for the growing impact of Parkinson’s disease in our society. Different genes distributed across the human genome have been associated with Parkinson’s disease, including *GBA*, *ADH1C*, *TBP*, *SCA17*, *HDL4*, *ATXN2*, *MAPT*, *SNCA*, *PARK1-22*, *LRRK2*, *PINK1*, *CHCHD2*, *c-Abl kinase*, *UCHL1*, *APOE*, and many others [10,11]. All these genes are under the influence of the epigenetic machinery (DNA methylation, chromatin remodeling, histone modifications, and miRNAs) that regulate their expression in different tissues and may contribute to selective nigrostriatal dopaminergic neurodegeneration.

The introduction of L-DOPA in the 1960s represented a breakthrough in the treatment of Parkinson’s disease, and it continues to be the most effective symptomatic therapy in Parkinsonian disorders [12]. Levodopa (L-DOPA) is the natural isomer of the amino acid D,L-dihydroxyphenylalanine which was isolated from the bean of *Vicia faba* in the early 1910s by Torquato Torquati. Its chemical structure was defined by Markus Guggenheim in 1913; and in 1938, Peter Holtz discovered the enzyme L-dopadecarboxylase, which converts L-DOPA into dopamine, and which can be transformed into noradrenaline by the enzyme dopamine- $\beta$ -hydroxylase. Both catecholamines are important neurotransmitters involved in different higher activities of the central nervous system. Other relevant scientists involved in the introduction of L-DOPA as a therapeutic option for Parkinson’s disease, as elegantly described by Oleh Hornykiewicz [13], were Kathleen Montagu, Weil-Malherbe and Bone, Carlsson, Sano, Cotzias, Dahlström and Fuxe, Moore, Lloyd and Calne, among others. In addition to dopamine precursors (L-DOPA), other symptomatic treatments for PD include dopamine agonists (amantadine, apomorphine, bromocriptine, cabergoline, lisuride, pergolide, pramipexole, ropinirole, rotigotine), monoamine oxidase (MAO) inhibitors (selegiline, rasagiline), and catechol-O-methyltransferase (COMT) inhibitors (entacapone, tolcapone) [14]. The initial complication of long-term L-DOPA therapy is the “wearing-off” phenomenon, [15,16] together with motor fluctuations and dyskinesia, which develop during the use of both L-DOPA and dopamine agonists [12,17]. Diverse dopaminergic and nondopaminergic pharmacological approaches have been developed to manage such complications, including novel L-DOPA formulations, COMT inhibitors (opicapone), dopamine agonists, adenosine A2A antagonists (istradefylline, preladenant, tozadenant), glutamatergic N-methyl-d-aspartate (NMDA) antagonists, serotonergic agents (eltopazine), and glutamate mGluR5 modulators (mavoglurant), with controversial results [18,19]. Polypharmacy with antidepressants, antipsychotics, urological drugs, analgesics, antihistaminics and cholinesterase inhibitors also contributes to severe complications

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associated with the anticholinergic burden in Parkinson's disease [20]. Furthermore, gastrointestinal complications (constipation, sialorrhea, dysphagia, difficulty in mastication, choking/aspiration) [21], cardiovascular problems [22], neuroendocrine changes and psychiatric disorders are frequent in Parkinsonian patients chronically treated with conventional antiparkinsonian drugs [14,21].

The onset of these complications is also influenced by the genomic background of the patients [11]; and the efficacy and safety of the drugs currently consumed by those who suffer a Parkinsonian disorder is highly dependent on their pharmacogenomic profile [23]. Genes involved in the pharmacogenetic network include pathogenic, mechanistic, metabolic, transporter and pleiotropic genes, and all these genes are also under the influence of potential epigenetic aberrations [24-26]. In recent years novel evidence has demonstrated the impact of pharmacogenetics on the efficacy and safety of most antiparkinsonian drugs [14,27-30]. In the particular case of L-DOPA, the *ANKK1*, *BDNF*, *LRRK2*, and *PARK2* genes are pathogenic genes potentially involved in its effects. The *CCK*, *CCKAR*, *CCKBR*, *DRD1*, *DRD2*, *DRD3*, *DRD4*, *DRD5*, *GRIN2A*, *GRIN2B*, *HCRT*, *HOMER1*, *LMO3*, and *OPRM1* genes are mechanistic genes whose products influence L-DOPA efficacy and safety. L-DOPA is a substrate of enzymes encoded by the *COMT*, *CYP1A2*, *CYP2B6*, *CYP2C19*, *CYP2D6*, *CYP3A4*, *CYP3A5*, *DBH*, *DDC*, *G6PD*, *MAOB*, *TH*, *UGT1A1*, and *UGT1A9* genes responsible for its metabolism. *SLC6A3* is the major transporter of L-DOPA; and *ACE*, *ACHE* and *APOE* are pleiotropic players in L-DOPA effects [14]. *ADORA2A* SNPs and *HOMER1* variants may be associated with L-DOPA-induced dyskinesia and psychotic symptoms [31,32]. A haplotype integrating -141Clns/Del, rs2283265, rs1076560, C957T, TaqIA and rs2734849 polymorphisms at the *DRD2/ANKK1* gene region might also be associated with L-DOPA-induced motor dysfunction [33]; and *SLC6A3* is a genetic modifier of the treatment response to L-DOPA in Parkinson's disease [34].

Since the "wearing-off" phenomenon and additional complications related to the chronic use of antiparkinsonian drugs represent a major concern for patients and the medical community, some voices claim for changes in the conceptualization of Parkinson's disease and its treatment, as well as some other neuropsychiatric disorders [35-37].

It is obvious that the growing prevalence and incidence of Parkinson's disease for the past 50 years must be associated with environmental factors which demand better epidemiological scrutiny and consequent preventive programs to halt disease progression, especially at a pre-symptomatic stage. If this is assumed by health authorities and the scientific community, then new challenges should be raised in relation to the pathogenesis and treatment of Parkinson's disease, if we do not want to experience a situation similar to that of schizophrenia (another disease related to a cerebral dopaminergic dysregulation), in which the excess of antipsychotics/neuroleptics leads to a disabling extrapyramidal syndrome after years of neuroleptic treatment.

Under these circumstances, it is imperative to characterize biomarkers for the pre-symptomatic identification of the population at risk of suffering Parkinson's disease, and to design novel preventive strategies as well as alternative therapeutics devoid of the long-term complications posed by conventional antiparkinsonian drugs. Some attempts have been made with novel compounds in recent times. The revival of some classic natural products, rich in L-DOPA (e.g. *Mucuna pruriens*, *Vicia faba*), has also been proposed; and new applications have been submitted to the European Patent Office in this regard, with selective dopaminergic neuroprotectants to prevent neurodegeneration [38]. An example of this is E-PodoFavalin-15999 (Atremorine®), a novel biopharmaceutical compound, obtained by means of non-denaturing biotechnological procedures from

structural components of *Vicia faba* L., for the prevention and treatment of PD [38-40]. Preclinical studies (*in vitro*) revealed that Atremorine is a powerful neuroprotectant in (i) cell cultures of human neuroblastoma SH-SY5Y cells; (ii) hippocampal slices in conditions of oxygen and glucose deprivation; and (iii) striatal slices under conditions of neurotoxicity induced by 6-OHDA. *In vivo* studies showed that Atremorine (i) protects against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced dopaminergic neurodegeneration; (ii) inhibits MPTP-induced microglia activation and neurotoxicity in substantia nigra; and (iii) improves motor function in mice with MPTP-induced neurodegeneration [38,39]. Clinical studies in untreated patients who receive Atremorine for the first time (never treated before with antiparkinsonian drugs) revealed that Atremorine enhances dopaminergic neurotransmission and increases by 200-500-fold plasma dopamine levels. In patients chronically treated with L-DOPA or other antiparkinsonian drugs, Atremorine induces a dopamine response of similar magnitude to that observed in previously untreated patients. Atremorine is also a powerful regulator of noradrenaline and pituitary hormones such as prolactin and growth hormone, which are under supra-hypothalamic control of dopaminergic neurotransmission. In addition, this dopaminergic response is associated with the pharmacogenetic profile of the patients [40]. The Atremorine-induced dopamine response is genotype-dependent and is influenced by pleiotropic gene variants, such as *APOE*, and *CYP2D6*, *CYP2C19*, *CYP2C9* and *CYP3A4/5* pheno-genotypes which influence L-DOPA metabolism as well as other components present in the complex composition of E-PodoFavalin-15999 [40].

Modern Neuroscience must embrace the idea that most brain disorders require more neuroprotection and fewer symptomatic repressors. Unfortunately, the history of Neuropsychopharmacology is a history of chemical symptomatic repression with delayed consequences for patients and society in terms of chronic disability, family burden, and health costs. In the particular case of Parkinson's disease, future challenges are (i) a better insight into the pathogenesis of premature dopaminergic neurodegeneration, (ii) the identification of biomarkers for an early diagnosis, (iii) the implementation of preventive programs to halt disease progression at pre-symptomatic stages; and (iv) the development of novel antiparkinsonian drugs with specific neuroprotective effects on the dopaminergic system.

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