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Parkinson's Disease

Understanding Pathophysiology and Developing Therapeutic Strategies

Edited by Sarat Chandra Yenisetti

PARKINSON'S DISEASE - UNDERSTANDING PATHOPHYSIOLOGY AND DEVELOPING THERAPEUTIC STRATEGIES

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http://dx.doi.org/10.5772/intechopen.70111
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Notice

First published in London, United Kingdom, 2018 by IntechOpen
eBook (PDF) Published by IntechOpen, 2019
IntechOpen is the global imprint of INTECHOPEN LIMITED, registered in England and Wales, registration number: 11086078, The Shard, 25th floor, 32 London Bridge Street
London, SE19SG – United Kingdom
Printed in Croatia

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library

Additional hard and PDF copies can be obtained from orders@intechopen.com

Parkinson's Disease - Understanding Pathophysiology and Developing Therapeutic Strategies
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p. cm.

Print ISBN 978-1-78923-152-6

Online ISBN 978-1-78923-153-3

eBook (PDF) ISBN 978-1-83881-459-5

Meet the editor

Dr. Sarat Chandra Yenisetti is an Associate Professor and Head of Drosophila Neurobiology Laboratory in Department of Zoology, Nagaland University (Central), Nagaland, India. He completed M.Sc. from Bangaluru University, India and was awarded Ph.D. from Kuvempu University, India. Dr. Sarat obtained post-doctoral training in "modelling Parkinson's disease using Drosophila" from Neurogenetics, National Institute of Neurological Disorders and Stroke (NINDS) of National Institutes of Health (NIH), Bethesda, USA and University of Regensburg, Germany. His laboratory is well funded through multiple research grants from Department of Biotechnology (DBT), India, University of Grants Commission (UGC), India and Department of Science and Technology (DST), India, that focuses on Drosophila approaches to understand Parkinson's disease associated neurodegeneration and identification of novel therapeutic targets which may help to reduce the burden of PD in human. Sarat visited USA, Japan, Germany, Taiwan, South Korea, United Kingdom, Brazil, Canada to participate in multiple academic assignments.

Contents

Preface

Parkinson's disease (PD) is the second most common neurodegenerative disorder results due to loss of dopamine producing brain cells. It has been speculated that gene environmental interaction is critical for the onset of PD and studies from model organisms substantiate this idea. Knowledge relating to PD condition has been known since 5000BC from ancient Indian civilization (named as KAMPAVATA), however no effective therapeutic strategies are available till today- once again illustrates human limitations in understanding sports of nature and countering them, if necessary. Therefore it is pertinent and important for neurobiologists to work further by taking advantage of modern scientific methods to diagnose the PD condition at early stage of dopaminergic degeneration and develop appropriate therapeutic strategies. Efforts in this direction are worthy as they will reduce the burden of PD among elderly, who are already burdened with age related systemic degenerative processes. Present book: **"Parkinson's Disease - Understanding Pathophysiology and Developing Therapeutic Strategies"** is a humble effort in that progressive direction.

My laboratory in India efforts at understanding and answering fundamental questions relating to dopaminergic degeneration/protection and sexual dysfunction relating to PD using *Drosophila* model. Hence this project excited me and importantly provided an opportunity to know more about multiple facets of PD, in particular futuristic possibilities in developing neuroprotective therapeutic strategies.

Understanding the cause(s) and pathophysiology is crucial to develop therapeutics to a disorder. To realise this aspect, the book is organised in such a way that: first section comprises the articles relating to etiology and pathophysiology of Parkinson's disease and second part includes articles concerning to developing effective therapeutic strategies and challenges and new developments to overcome the hurdles. Such an organisation helped story narration to unfold in a smooth, interesting and fruitful fashion. Both the sections have articles relating to basic and applied aspects of the PD. Hence it should be of relevance and interest to both basic science researchers and clinicians.

I am thankful to publishing process manager of the book, Ms. Martina Usljebrka for constant and fantastic support.

As I am editing a book for first time, whole journey has been a humbling learning experience. I realised limitations of my limited understanding relating to various aspects of PD. I thank *IntechOpen*, Croatia for giving an opportunity to learn and update myself in an area of my research interest.

I sincerely opine that available information and knowledge of this book, will be of some help to common man, biomedical researchers and clinicians. Eventually this knowledge may comfort "to reduce the burden of neurological disease."

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Section 1

Parkinson's Disease: Etiology and Pathophysiology

Chapter 1

Sleep Disorders in Parkinson's Disease

Dursun Aygun

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.73520

Abstract

Sleep disorders in Parkinson's disease (PD) are common. They can develop due to many factors. PD symptoms like rigidity or tremor, some PD medications, restless legs syndrome, depression, nocturia, and degenerative changes in the brainstem can cause sleep disorders in PD. Sleep disorders in PD may occur during the day or at night. Sleep disorders can occur before or during the disease. Sleep disorders can impair patients' quality of life and worsen their symptoms. For this reason, it is very important to recognize these disorders and treat them appropriately. This chapter discusses the clinical features, diagnosis, comorbidities, management, and pathogenesis of sleep disorders in PD under the literature light. At the same time, it describes the most appropriate treatment considerations.

Keywords: Parkinson's disease, sleep disorders, rapid eye movement (REM), sleep behavior disorder, insomnia, daytime sleepiness

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disease characterized clinically by bradykinesia, resting tremor, postural instability, and rigidity [1]. Parkinson's disease is not only associated with motor symptoms but also with many non-motor symptoms such as sleep disorders, autonomic disorders, olfactory disorders, and psychiatric symptoms [2]. The spectrum of sleep disorders in PD is broad. In PD, the most common sleep disorders include insomnia [difficulty initiating sleep and its associated restless legs syndrome (RLS), as a reason for the difficulty of falling into sleep, sleep fragmentation, or early awakening], excessive daytime sleepiness (EDS), and rapid eye movement sleep behavior disorder (RBD) [2–4]. While most sleep disorders occur in the advanced stages of the disease, RBD and EDS can be observed in the early phase and even in the premotor phase [5]. A study reported that RBD occurred in the premotor phase of the disease in 38% of 29 patients with PD [5]. On the other

hand, it has been reported that only one in four patients with PD develops RBD before the disease [6]. Sleep disorders, which affect more than half of the PD patients, can significantly affect the quality of life [7]. It has been reported that the prevalence of sleep disorders in patients with PD is 2–3.5 times higher than in healthy controls [6]. In the pathogenesis of sleep disorders in PD, many etiological factors affecting mainly the sleep-related structures play a role [3, 7]. In addition, in the PD, secondary factors that can negatively affect sleep include pharmacological agents (e.g., selective serotonin reuptake inhibitors-SSRI, serotonin-norepinephrine reuptake inhibitors (SNRI)), nocturnal motor symptoms (e.g., akinesia and dystonia), nocturia, depression, cognitive impairment, and pain [3, 7, 8]. Each of the sleep disorders in PD can be seen individually or more than one sleep disorder can be seen in the same patient at the same time [3]. A recent meta-analytic study found that there was a significant overlap of various sleep-related symptoms in the patients with PD [3]. The study reported that the coexisting prevalence of two out of three sleep-related symptoms (EDS, PD-related sleep problems and RBD) was approximately 20%. The coexistence of all these three symptoms is 12.2% [3].

In this chapter, sleep disorders in patients with PD were classified, and their clinical features, pathophysiology, diagnostic assessment, and management were reviewed. First, a diagnosis of each sleep disorder was given separately, and at the end of the chapter, a general assessment of sleep disorders in the PD was given. In addition, the deep brain stimulation (DBS) in the treatment of sleep disorders in PD was processed at the end of the chapter. This chapter only addresses sleep disorders related to PD.

2. Classification of sleep disorders in Parkinson's disease

Sleep disorders in PD may occur during the day or at night. In PD, sleep disorders can be classified into three major categories such as abnormal behaviors and events during or around sleep (e.g., RBD), inability to sleep (e.g., insomnia), and EDS (**Table 1**) [6, 8]. These three categories of sleep disorders can be seen separately or together [6].

Categories	Sleep disorders
Parasomnia	REM parasomnias (e.g., RBD)
	NREM parasomnias (e.g., sleepwalking, confusional arousals, and sleep terrors)
Inability to sleep/sleeping difficulty	İnsomnia
	• Initial insomnia (i.e., difficulties initiating sleep)
	• Maintenance insomnia (i.e., sleep fragmentation)
	• Terminal insomnia(i.e., early awakening)
Sleepiness	EDS

REM: rapid eye movement; RBD: rapid eye movement sleep behavior disorder; NREM: Non-rapid eye movement; EDS: excessive daytime sleepiness.

Table 1. Classification of sleep disorders in Parkinson's disease.

3. Parasomnias in Parkinson's disease

In PD, parasomnias are quite common, and REM parasomnias are more common than those in NREM [6]. As REM parasomnia in PD, RBD can be seen in near two-thirds of patients [9]. In PD, non-NREM (NREM) parasomnias can include sleepwalking, confusional arousals, and sleep terrors. However, NREM parasomnias are not a frequent cause of sleep disorders in PD [6].

4. Rapid eye movement sleep behavior disorder

4.1. Clinical features of RBD

Rapid eye movement sleep behavior disorder is a parasomnia characterized by dream-related vocalizations such as screaming, talking, and shouting and/or complex motor movements such as kicking, and punching with episodic loss of atonia during REM sleep [10, 11]. In severe cases, patients may be able to jump out of bed and injure themselves [6]. It has been reported that the prevalence of RBD in PD patients varies from 20 to 72% [9]. However, the most recent meta-analysis revealed that the overall prevalence of RBD symptoms in PD was 23.6% compared to 3.4% in control [12]. In PD, the frequency of RBD in the stages of the disease is reported differently in studies. Although, in PD, RBD is a sleep disorder that can be seen before the disease, it can also occur at the same time or after the disease in the majority of patients [6]. It has been reported that RBD is associated with some specific features such as age, gender, motor sub types, cognition, disease duration, disease severity, antiparkinsonian medication, and autonomic dysfunction in PD patients [9]. It has been known that some of the abovementioned features such as cognitive and autonomic dysfunction in PD patients with RBD are more common than those without RBD. In our study, 57.6% of patients with PD had a clinical RBD diagnosis [13]. The frequency of clinical RBD was unrelated to motor subtypes of PD [13]. However, we found a weak correlation between clinical severity (i.e., the unified Parkinson's disease rating scale-UPDRS and Hoehn–Yahr-HY stage scores) of PD and severity of clinical RBD in the non-tremor dominant-NTD subtype but not in the tremor dominant-TD subtype. In our study, RBD symptoms appeared before motor symptoms in approximately one-third of PD patients with RBD [13].

4.2. Diagnosis of RBD in PD

The diagnosis of RBD can be based on a questionnaire or clinical manifestations without confirmation by polysomnography (PSG) [2, 13, 14].Therefore, a detailed history of complex motor behaviors and vocalizations during REM sleep is very important for a clinical diagnosis of RBD. However, for the objective diagnosis of RBD, complex motor behaviors during REM sleep and the presence of REM sleep without atonia should be confirmed by PSG [11]. Additionally, this sleep disturbance should not be better explained by another disorder [11]. PSG can detect increased chin muscle tone (i.e., absence of atonia) by the submental EMG or increased phasic muscle activity by the limb EMG during REM sleep [2, 15]. Thus, PSG is not required for the clinical diagnosis of RBD [13, 14]. It has been reported that a total score of 6 or

higher obtained from 'the RBD screening questionnaire (RBDSQ)' used for the clinical diagnosis of RBD may strongly support (sensitivity = 0.842, specificity = 0.962) the diagnosis [16].

4.3. Pathophysiology of RBD in PD

REM sleep is regulated by the brain stem, hypothalamus, thalamus, substantia nigra, basal forebrain, and frontal cortex [17]. The brain stem structures involved in REM sleep include the pedunculopontine nucleus (PPN), retro-rubral nucleus, subcoeruleus/sublateral dorsal nucleus, and medullary magnocellular reticular formation (MRF) [17]. These brain stem structures provide REM atonia by inhibiting the spinal motor neurons through direct and indirect pathways (the reticular formation as an intermediate station inhibiting the spinal motor neurons) [4, 18, 19]. Thus, these two inhibitory pathways play a role in skeletal muscle atonia during REM sleep [4, 18, 19]. The PPN and the retro-rubral nucleus also act as a phasic generator circuitry [18]. It is well known that the PPN/laterodorsal tegmental nuclei (LDN) have both cholinergic activity and non-cholinergic (e.g., GABAergic) activity. So the PPN/LDN also contains glutamatergic and GABAergic neurons [20]. On the other hand, the cholinergic neurons in the PPN/LDN innervate the pontine reticular formation (PRF), MRF, and thalamus [19, 20]. Thus, descending projections of the PPN stimulate the inhibitory interneurons via the reticulospinal neurons and inhibit directly the motor neurons in the spinal cord and modulate the activations of the mesencephalic locomotor region (**Figure 1**) [4, 19, 21, 22]. It has been reported that inhibition of GABA activity in the PPN, an important part of locomotion, results in explosive motor behavior [23]. In addition, the ascending projections to the thalamus from the PPN modulate the *sleep–wake cycle.* It has been reported that RBD emerges as a result of the involvement of the atonia system and locomotor regions [4, 24]. Experimental studies suggest that the locomotor regions are activated during the REM sleep and suppress locomotor activity [24]. Thus, neuronal dysfunction in RBD is mainly in the PPN/LDN and the sublaterodorsal nucleus (SLD)/pre-coeruleus (REM-on areas) directly and indirectly inhibiting the spinal motor neurons (**Figure 1**) [2, 19, 20, 23]. Finally, the PPN/LTD produces both skeletal muscle atonia (together with SLD) and decreased locomotion during REM sleep [4, 19]. As a result, by the degeneration of these neuronal structures involved in the control of REM atonia in RBD in PD, the functions of medullary MRF which is an intermediate station are also significantly affected [4, 17]. In addition, it is clear that the degeneration of the brain stem areas that depress the locomotion during REM sleep also causes the complex motor movements (increasing in locomotion) of the RBD. As a result, loss of function of these brainstem structures regulating REM sleep causes the clinic of RBD to occur (**Figure 1**) [4, 17, 20].

It has been reported that in the first phase of the Braak staging, Lewy body pathology begins at the dorsal motor nucleus of the medulla oblongata. In the second stage, pathology progresses upwards and affects the magnocellular reticular nucleus, sublateral dorsal nucleus, and olfactory structures. The PPN is degenerated by Lewy body pathology in the third phase of the Braak staging [17]. Thus, RBD in PD is caused by Lewy body pathology involving the brain stem structures that play a role in the regulation of REM sleep. It has been reported that there are "REM-on" and "REM-off" zones in the brain stem of the rats [25]. On the other hand, the relationship between hypocretin and REM sleep remains a controversial issue [26, 27].

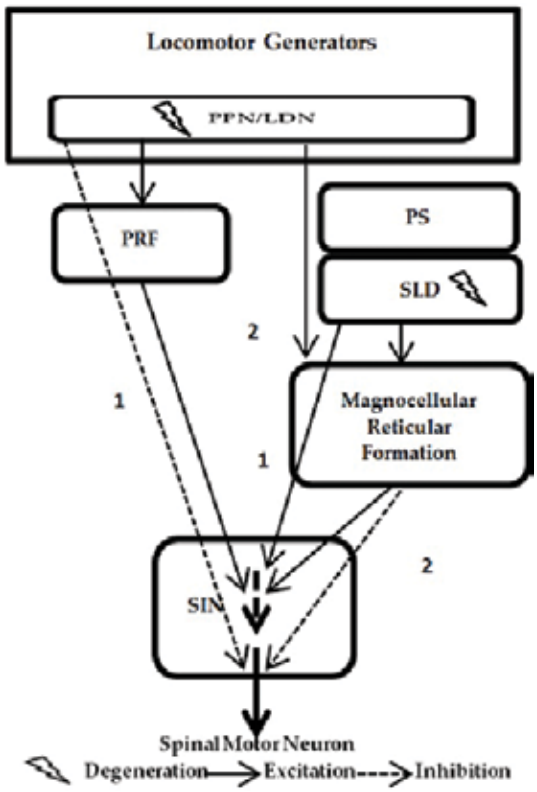

Figure 1. Pathophysiology of rapid eye movement (REM) sleep behavior disorder in PD. PD: Parkinson's disease; PPN/LDN: pedunculopontine nucleus/laterodorsal tegmental nucleus; PS: pre-coeruleus; SLD: sublaterodorsal nucleus; PRF: pontine reticular formation; MRF: medullary magnocellular reticular formation; SIN: spinal interneuron. 1. Direct route; 2. indirect route inhibiting the spinal motor neurons via the reticular formation. In REM sleep, muscle atonia occurs following the activation of the medullary magnocellular and the pontine reticular formations inhibiting the spinal motor neurons [4, 19]. There are descending connections from the PPN to the pontine and medullary reticular formations, and the spinal cord. There are also descending connections from SLD to the MRF and the spinal motor neurons. Thus, it may be considered that inhibition of muscle tone arises both from activating the retikülospinal neurons in both the PRF and the MRF of the cholinergic neurons in the PPN and from activating the retikülospinal neurons in the MFR of the neurons in the SLD [4, 19].

A review article reported that hypocretin can stabilize the REM-on and REM-off pontine areas in the brain and can also participate in spinal motor neuron inhibition [25]. A study suggested that decreased hypocretin levels were associated with RBD due to loss of stabilization in the REM regulation of muscle atonia [26].

4.4. Treatment of RBD in PD

Currently, the two most commonly used drugs in the treatment of RBD are melatonin and clonazepam. Melatonin is the second choice in the treatment of RBD and is usually an alternative option in patients with sleep apnea or mental impairment. It is recommended to take melatonin between 3 and 12 mg doses before bedtime [17]. The mechanism of action of melatonin

in RBD is still unclear. However, melatonin may resolve RBD-related complaints by decreasing muscle tone during REM sleep [28, 29]. Melatonin has many side effects such as daytime sleepiness, morning headache, and mental deterioration and is usually associated with high doses [17]. Clonazepam is widely used in RBD and doses between 0.25 and 1.0 mg taken before bedtime are sufficient for treating the RBD symptoms [17]. Like melatonin, the mechanisms of action of clonazepam in RBD are not fully clear. However, it has been believed that clonazepam modulates dreaming/complex motor behaviors at supratentorial levels [17]. Clonazepam may worsen symptoms of sleep apnea and mental disorder [30]. It has been reported that the most important side effects of clonazepam are sedation, imbalance, and sexual dysfunction [17]. If these two treatments are not adequately answered or there is a contraindication, rivastigmine, donepezil, pramipexole, and paroxetine may be tried [8]. One study showed that rivastimine significantly reduced the frequency of RBD episodes at the end of the third week in 12 PD patients with classical treatment-resistant RBD [31]. The authors suggest that this effect is related to the peripheral cholinergic action of rivastigmine [31]. In a recent review, it has been reported that there are limited evidences indicating that drugs such as zopiclone, desipramine, clozapine, carbamazepine, and sodium oxybate may be effective in RBD [8].

5. Insomnia

5.1. Clinical features of insomnia

Insomnia is defined as difficulties initiating sleep (initial insomnia), sleep maintenance problem (i.e., frequent awakenings/sleep fragmentation) or early awakening [2, 6]. In studies, it has been reported that the frequency of insomnia in patients with PD varies from 27 to 80% [32–35]. It has been reported that the most common types of insomnia in PD patients are sleep fragmentation (81%), and early awakenings (terminal insomnia; 40%) [8]. It has been reported that insomnia may occur alone or accompany comorbid mental or systemic illnesses, and it is associated with disease duration and female gender [6]. Sleep fragmentation is defined as a deterioration of sleep integrity (i.e., waking up several times during the night), and it leads to a lighter sleep or wakefulness [2]. In studies, it has been reported that sleep fragmentation is the most common sleep disorder (74–88%) in patients with PD [36, 37].

5.2. Diagnosis of insomnia in PD

In the diagnosis of insomnia in PD, the clinical history including the stages (defined above) of insomnia and its associated factors are essential. For example, the factors associated with initial insomnia should be learned from the clinical history because the identification of factors associated with insomnia is necessary for the treatment plan. **Table 2** shows the factors associated with insomnia [2, 6]. For example, for the diagnosis of RLS, as a reason for the difficulty of falling into sleep, clinical assessment (sleep history) is sufficient. Thus, patients should be asked for the features in the definition mentioned below for the diagnosis of RLS [6]. In contrast to idiopathic RLS, family history of RLS is less frequent in PD [6]. Polysomnography

and actigraphy can be used to detect the objective findings of the insomnia [15]. It has been reported that insomnia's PSG findings may be an increase in the number of brief EEG arousals—or arousal index, number of stage shifts to stage 1 or wake, wake time after sleep onset (WASO), and percentage of stage 1 sleep [2]. The actigraphic findings of insomnia include the presence of irregularity in sleep onset and increased number of awakening times during the night [15]. One review has been reported that studies comparing PSG to actigraphy in insomnia show that PSG and actigraphy have no significant difference in showing the measurements of WASO, total sleep time (TST), and sleep efficacy [38].

5.3. Pathophysiology of insomnia in PD

In the pathogenesis of insomnia in PD, damage of the brain regions associated with sleep has an essential role [6]. In addition to PD pathophysiology, motor symptoms of PD, medications, mood disorders, pain, physical disability (lack of exercise), and poor sleep hygiene are other factors contributing to the pathogenesis of insomnia in PD [6, 8]. Thus, the etiology of insomnia in PD is multifactorial, and it can include intrinsic sleep disorders such as altered dream phenomena, RBD, restless leg syndrome (RLS), and periodic leg movements in sleep-PLMS), PD symptoms such as nocturnal akinesia and rigidity, pain, nocturia, and psychiatric comorbidities such as anxiety, and medications (**Table 2**) [6, 8].

The restless legs syndrome, which is a cause of insomnia (by making sleeping difficult), is characterized by an urge to move the legs typically accompanied by tingling, paresthesia, or unpleasant sensations in the legs, which is worsened during periods of inactivity and improved by voluntary movement [2, 6]. In RLS, symptoms are often worse in the evening or at night [2, 6]. It has been reported that the prevelance of RLS in PD varies from 0 to 50% [6]. It has been reported that there has a role of central dopaminergic depletion in the pathophysiology

Factors	Initial insomnia	Maintenance insomnia
Psychiatric comorbidities	Depression and anxiety	Depression and anxiety
Intrinsic sleep disorders	RLS	RBD
Medications	Selegiline, amantadine, caffeine, SSRI	Excessive dopaminergic therapy
Sleep-related movement disorders	RLS, painful leg cramps	Periodic leg movements
Pain	Back pain	Dystonia-related pain
PD symptoms	Annoying tremor	Nocturnal akinesia/difficulty turning right and left in bed
Others	Non-motor fluctuations, systemic illnesses	Nocturia, systemic illnesses

PD: Parkinson's disease; RBD: rapid eye movement sleep behavior disorder; SSRI: selective serotonin reuptake inhibitors; RLS: restless legs syndrome.

Table 2. Factors associated with insomnia in PD.

of both RLS and PD [2]. On the other hand, it has been reported that the most common causes of wakings during the night are nocturia and difficulty turning right and left in bed [6]. Studies have shown that the frequency of sleep fragmentation in PD is related to the clinical severity of the disease, as evidenced by the UPDRS and Hoehn and Yahr (HY) scales [39, 40].

5.4. Treatment of insomnia in PD

The first step in the treatment of insomnia must be to determine the type (i.e., initial, of maintenance, or terminal) of insomnia and the possible factors affecting it such as medications that can cause insomnia [2, 8]. A treatment plan should then be made. For example in initial insomnia, behavioral therapies such as photo therapy, sleep hygiene measures, relaxation, and cognitive therapy may be recommended first and medications such as hypnotics (e.g., Zolpidem, eszopiclone-newer benzodiazepine receptor agonist) or sedating anti-depressants (e.g., mirtazapine and trazodone)may be given if necessary [6, 8, 15, 41]. It has been recommended that hypnotics should be avoided in patients with sleep apnea syndrome [15]. In initial insomnia, melatonin receptor agonists such as ramelteon may also be helpful [8, 15]. Sedating anti-depressants may also be used for maintenance insomnia [8]. However, clonazepam (long-acting sedative) taken at bedtime may be a good option for the treatment of maintenance insomnia (i.e., sleep fragmentation) due to PLMS [42]. If insomnia is due to motor disability of PD, evening dose of controlled-release levodopa to prevent immobility improves insomnia [8]. It has been reported that dopamine agonists may influence the subjective symptoms of insomnia [2]. On the other hand, because of central dopaminergic depletion has a role in the *pathophysiology* of both RLS and PD [2], the dopamine agonists (e.g., pramipexole and ropinirole) used in idiopathic RLS can also be recommended in the treatment of RLS in PD [2, 6]. In addition, since dopamine agonists reduce RLS and PLMS, they may be useful in decreasing sleep fragmentation [43]. Although levodopa is effective in RLS, it is not recommended because it causes side effects such as RLS augmentation and morning rebound [44]. If there is an additional symptom associated with RLS, such as pain, treatment options may be include pregabalin, gabapentin, opiates, and benzodiazepines [45, 46]. In PD, PLMS is less common and its frequency increases in the advanced stages of the disease [47].

Atypical antipsychotics are not recommended for the treatment of insomnia without a psychotic disorder [15].

6. Excessive daytime sleepiness

6.1. Clinical features of EDS

Excessive daytime sleepiness is a chronic or episodic sleepiness seen throughout the day in PD patients [2]. Anxiety and depression, cognitive dysfunction, changes in sleeping habits, changes in circadian rhythm, the side effects of medications that can produce sleep attacks such as dopamine agonists, and concomitant systemic diseases can cause sleepiness [2, 48]. Also these factors can cause fatigue [2]. Studies have reported that EDS is very common in PD. Verbaan et al. [49] found that compared to controls (10%), 43% of PD patients had

EDS. One study found that EDS was related to age and male gender [50]. Also, other sleep disorders such as PLMS, and sleep fragmentation which cause the deterioration of night sleep quality may be the other causes of EDS [6, 15].

6.2. Diagnosis of excessive daytime sleepiness in PD

In patients describing the symptoms of EDS, it is very important to determine the level of sleepiness. The Epworth Sleepiness Scale (ESS) is widely used in the evaluation of EDS. Thus, ESS (score greater than 10) is a useful scale for the subjective assessment of sleepiness in patients with EDS [51].The ESS contains eight items, and each item is rated as maximum three points. A higher score means more sleepiness level. In addition, there are objective tests such as multiple sleep latency test (MSLT) and maintenance of wakefulness test (MWT) for assessment EDS. The MWT is evaluation used as a polysomnographic measurement of EDS. The MSLT is measured after a PSG performed in the night to assess nighttime sleep quality and quantity [52]. One study found that the risk (sensitivity 75%) of traffic accidents increased in PD patients with an ESS score greater than 7 [53].

6.3. Pathophysiology of excessive daytime sleepiness in PD

It has been reported that there are three main causes of sleepiness in PD; (1) deterioration of night sleep quality, (2) neurodegeneration of sleep–wake-related brain regions, as a result of disease pathology, and (3) the side effects of antiparkinsonian medications [6, 32]. However, many of the abovementioned causes may be related to EDS. For this reason, it is necessary to consider these causes in the diagnosis and treatment of EDS.

6.4. Treatment of excessive daytime sleepiness in PD

The first step in the treatment of EDS should be the correction of underlying conditions [8]. For example, it may be useful to treat the conditions that disturb sleep quality at night or to arrange medications that cause daytime sleep episodes. After that, pharmacological treatment options for EDS should be considered. Nonpharmacological treatment approaches (e.g., good sleep hygiene, bright light therapy) can be performed in the treatment of mild to moderate EDS cases [54]. Modafinil is widely used for the symptomatic treatment of EDS, which appears to stimulate catecholamine production [55]. Common side effects of modafinil are insomnia, headache, dry mouth, dizziness, nausea, nervousness, and depression [56]. A review has reported that sodium oxybate and methylphenidate have inadequate evidence that they are effective in the treatment of EDS in PD [8]. Amantadine and selegiline are reported to have an alerting effect [2]. Thus, amantadine and selegiline may be preferentially used in PD patients with EDS.

7. Diagnostic assessment of sleep disorders in PD

The history taken from the patient and its neighbors (e.g., partner) is very important in assessing sleep disorders in PD. The type of sleep disorder should be identified in the history, and information about possible related factors should be obtained from the history. In PD, general

and specific scales can be used to investigate the subtype of sleep disorder and to determine its severity. Objective methods can be used to further investigate the diagnosis of these disorders. Further investigative techniques include sleep recording methods such as actigraphy or PSG. Polysomnographic findings of each sleep disorder have been explained in the relevant section. In addition, information about screening scales used in each sleep disorder has been described in the relevant section.

Actigraphy is an electrophysiological device that measures the movements of the patient during sleep by recording from wrist or ankle for many days. Actigraphy evaluates indirectly the circadian sleep–wake patterns [15]. It is especially used in circadian rhythm disorders or insomnia and prolonged daytime sleepiness [15].

8. Deep brain stimulation in the treatment of sleep disorders in PD

Studies investigating the effect of DBS in the treatment of sleep disorders in PD patients showed that DBS improved the sleep scales and quality [57–60]. Baumann-Vogel et al. [58] found that subthalamic nucleus (STN) DBS-enhanced subjective sleep quality, reduced sleepiness measured by the Epworth sleepiness scale, and reduced sleep fragmentation shown by actigraphy recordings. However, the authors observed that subthalamic DBS was not improved REM sleep features [58]. Similarly, Cicolin et al. [59] reported that RBD symptoms did not benefit from STN DBS. On the other hand, Chahine et al. [61] reported that STN DBS improved significantly symptoms of RLS in PD patients. The effect of PPN DBS on sleep disorders in PD has been investigated in several studies [57, 62]. One study showed that PPN DBS improved sleep quality and reduced EDS; however, it caused a reduction in REM latency and a relevant increase in REM sleep [57]. In another study, it has been reported that PPN DBS improved the total duration and rate of REM sleep [62]. As a result, DBS seems to be beneficial in the treatment of sleep disorders in PD because it seems to be useful in improving sleep quality. However, large-scale prospective studies are needed to understand the benefits of DBS in the treatment of sleep disorders in PD.

9. Conclusion

Sleep disorders in PD are common. In the pathogenesis of sleep disorders in PD, degeneration of the brain regions associated with sleep has an essential role. Sleep disorders in PD can impair patients' quality of life. For this reason, it is very important to recognize and treat sleep disorders in PD. The history taken from the patient and its neighbors (e.g., partner) is the first step in assessing sleep disorders in PD. Sleep scales and objective assessment methods can be used to further investigate sleep disorders. In addition to the type of the sleep disorder, its related factors (i.e., comorbidities) in PD should be determined from the sleep history of the patient. Symptomatic treatment of sleep disorder and correction of factors associated with it should be the next steps. The age of the patient and accompanying diseases should be considered when choosing medical drugs used for symptomatic treatment of sleep disorders.

Side effects of some medicines may be fatal in patients with comorbidities. For example, clonazepam used RBD may worsen symptoms of sleep apnea and mental disorder [30]. Further studies are needed to improve more specific treatments and better understand the pathophysiology of sleep disorders in PD.

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Chapter 2

A Description of Parkinson's Disease in People of African Origin

Marcelle Smith

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.73519

Abstract

With the increase in life expectancy of African populations, the burden of degenerative diseases such as Parkinson's disease (PD) has grown. Neurologists are noticing trends in the differences reported in the phenotype of PD among African populations compared to Caucasian counterparts. These differences are chiefly in age of onset and clinical presentation. This chapter focuses on different aspects of the presentation of Parkinson's disease, as they apply to African populations and those of African origin.

Keywords: Parkinson's, African, phenotype, Black

1. Background

African countries have been experiencing rapid changes with increases in life expectancy. This has increased the burden of age-related and neurodegenerative conditions such as Parkinson's disease (PD). Some of the earliest descriptions of Parkinsonian disorders can be traced back to Ancient Egypt, as early as 1350–1200 BC. However, not much is known about idiopathic Parkinson's disease (PD) in Black African populations. The classic description, as we know it, has been derived by studying predominantly Caucasian populations. For decades, there has been anecdotal evidence that the phenotype or description of PD may differ in people of African origin. This chapter focuses on various aspects of PD as they apply to African populations as well as those of African origin.

2. Incidence and prevalence

One of the earliest studies comparing the prevalence of Parkinson's disease was conducted at a hospital in New Orleans [1]. Records were reviewed over a 10-year period, from 1959 to 1969. The patient population was 75% Black. Only patients with a definite diagnosis of PD were included in the study. The study revealed a much lower prevalence of PD in Black patients compared to White patients (0.022 and 0.146%, respectively).

Mayeux and colleagues carried out a population-based study to determine the prevalence of Parkinson's disease in Washington Heights in New York [2]. The study was conducted from January 1988 to December 1993. A registry of patients with PD was created by advertising on radio and television. Patients with and without dementia were included in the study. The prevalence of PD was calculated at 99.4 per 100,000. This increased from 2.3 per 100,000 in patients younger than 50 years old to 787.1 per 100,000 in those older than 80 years old. The study demonstrated that age is a powerful risk factor for Parkinson's disease and that it affected men more than women and White people more than non-White people.

Van Eeden and colleagues conducted a study that aimed to determine the incidence of Parkinson's disease by ethnicity, age, and gender [3]. This was the first study of its kind. Newly diagnosed patients between 1994 and 1995 from a large health maintenance organization in Northern California, the Kaiser Permanente Medical Care Program, were included in the study. A total of 588 newly diagnosed with Parkinson's disease were identified from the membership data. These patients were diagnosed according to the Hugh's criteria/modified Core Assessment Program for Intracerebral Transplantation. There was an overall incidence rate of 13.4 per 100,000. This increased significantly over the age of 60. The mean age at diagnosis was 70.5 (38–91) for both men and women. White patients were found to be older at diagnosis compared to Black, Hispanic and Asian patients. The annual incidence of Parkinson's disease was 12% in people under 50 years old and 44% in those over 50 years old. Only 4% of cases overall had onset of disease before the age of 50. The rate of PD was 91% higher in men than in women.

An epidemiological study carried out by Wright Willis et al. in 2010 investigated the geographic and ethnic differences associated with Parkinson's disease [4]. This was a cross-sectional study of Medicare users in the United States, from 65 years and onward. The investigators found that the prevalence of Parkinson's disease in people over 65 years old was just less than 2%. The prevalence also increased with age, without reaching a plateau. A 50% lower prevalence was demonstrated in Black and Asian patients. Black patients appeared to have a higher PD-related morbidity than White patients. This finding has yet to be explained.

Several studies have been conducted in Africa; however, these have mostly been epidemiological studies. In the 1970s, Harries, a neurologist in Kenya, saw a total of 750 patients in his practice over a period of 5 years [5]. He observed that only 4% (27) of patients had a diagnosis of PD during this time. The mean age was fairly young, with an age range of 45–60 years.

Around the same time, Collomb, a British neurologist working in Senegal, compared the patients from his practice with patients he had seen previously in the United Kingdom [5]. He reported that, over a 10-year period, the prevalence of Parkinson's disease among both in and

out patients was less than 1%. He also noted that in patients with typical Parkinson's disease, 25% of the patients had a much slower disease progression than the patients he had worked with while in England.

Lombard and Gefland conducted a retrospective review of Black patients admitted with Parkinson's disease to a hospital in Harare, Zimbabwe, between 1973 and 1976 and compared them with admissions of White patients to Andrew Fleming Hospital in the same city [5]. Out of 82,000 Black patients admitted to hospital, 17 cases of PD were found, compared to 33 cases of PD out of 35,000 White patients admitted.

A systematic review was conducted in 2006, by Okubadejo, which reviewed all African studies published between 1944 and 2004 [6]. These studies originated from 13 African countries. The analysis revealed that the prevalence of PD in African populations appeared to be lower than their North American and European counterparts.

In 2010, the same group published results of a study that sought to investigate the clinical profile of Parkinson's disease in a population of patients in Lagos, Nigeria [7]. These results were extracted from a database collected over 10 years. Of the 124 patients with Parkinsonism, 98 (79%) had idiopathic Parkinson's disease, while 26 (21%) had secondary PD. The results showed a similar disease profile to European counterparts, although there were fewer patients with early onset disease (<50 years old) and family history. Only 1% of all patients had a family history of PD. The frequency of young onset PD was 16%. In terms of clinical presentation, 32% were tremor-predominant, 55% were mixed, and 14% had an akinetic-rigid presentation. These different clinical presentations were not compared for gender. An important observation was that, compared to European studies, there was a greater delay in diagnosis. One of the negative aspects of this study was that patients with secondary Parkinson's disease were not excluded from the study.

Of the first few studies that have come out of South Africa, most have been prevalence studies. Cosnett and Bill published an observational study in 1988, which included 2638 patients from three major hospitals in Durban, South Africa [8]. This was the first of its kind in South Africa. The prevalence of Parkinson's disease was determined by calculating the frequency of levodopa usage, as well as the number of patients diagnosed with Parkinson's disease. This was compared to the total number of patients seen at each hospital. To exclude recruitment bias caused by fewer Black people seeking medical care, investigators compared the prevalence of motor neuron disease and secondary Parkinson's. The rates of these illnesses were similar in both Black and White populations. The results showed a lower prevalence of PD in Black patients compared to White patients. One of the theories was that the lower life expectancy of the Black population in the area meant that Black people did not live long enough to develop PD.

3. Heredity and age of onset

To date, studies of Parkinson's disease in African populations have shown a lower incidence and prevalence compared to European and North American populations. The findings regarding the frequency of early onset Parkinson's disease (EOPD) in Black patients have been inconsistent. A

family history of PD is associated more frequently with a younger onset, but is found in a significant percentage of late onset PD (LOPD) as well. There is also a greater delay in diagnosis of PD in Africa. None of these earlier studies done in Africa looked specifically at whether PD patients had a family history. In recent years, there has been surge in research of Parkinson's disease in Africa.

In 2012, a group from the Neurology Department in a Western Cape Hospital, South Africa, conducted a study to just answer this question [9]. Van Der Merwe and others investigated the factors associated with early onset (EOPD) and late onset Parkinson's disease (LOPD). EOPD was defined as an age of onset (AOO) of 50 years old or younger, and LOPD as an age of onset over 50. The data were derived from a genetic study run over a period of 5 years. Three hundred and ninety-seven unrelated patients of different ethnic groups were recruited. The study reported a high incidence of early onset PD and significant family history in South African patients (34.8%). EOPD was found to be more frequent in Black (7.2%), White Afrikaner (39.7%), and mixed-ancestry participants (27.0%) compared to White English-speaking patients (24.3%). A positive family history was also associated with an earlier onset. However, a third of LOPD cases had a significant family history as well. This challenges the assumption that LOPD is purely sporadic. Gender had no measurable effect on age of onset. This was congruent with other recent literature (**Figure 1**).

Mahne et al. published a study in June 2016, which aimed to describe both clinical and genetic findings in a group of Black South African patients with Parkinson's disease [10]. All Black patients with PD who attended Steve Biko Academic Hospital were offered participation in the study. A total of 16 patients were included in the study. Three patients had a positive family history but only one of these patients had an identifiable genetic mutation, Parkin1. This

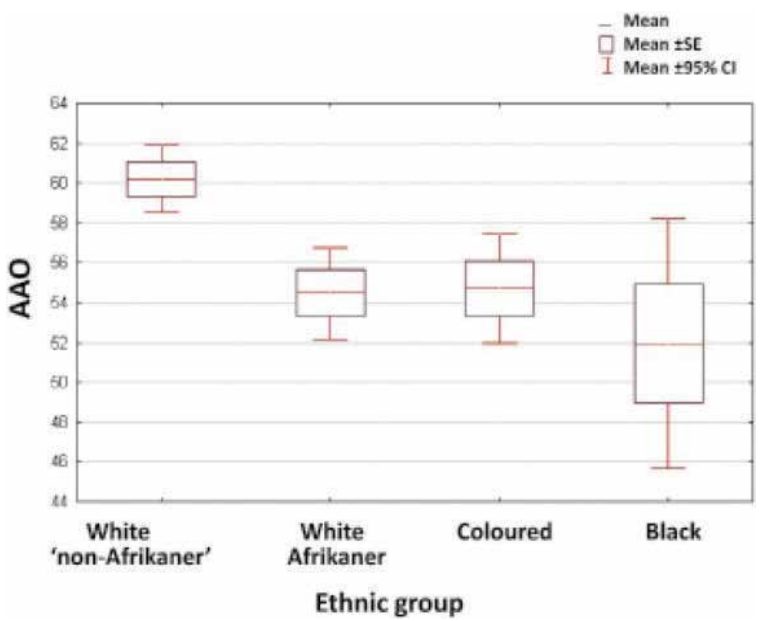

Figure 1. Box-and-Whisker plots of age of onset of PD versus ethnicity. Data are represented as means [9].

	Black (n = 35)			White (n = 11)			p-value
	Mean	Range	95% CI	Mean	Range	95% CI	
Age	60.8	51–76	55.8–65.8	67.2	44–83	61.6–72.8	0.089
AOO	54.31	12–78	49.6–59	60.7	43–78	53.5–67.9	0.164
TTDx	20.3	0–120	53.5–67.9	56.7	0–360	22.8–136.3	0.33
MMSE	25	15–90	20.9–29:2	24.6	13–30	20.9–28.3	1.0
H&Y	2.5	1–5	2.2–2.8	2.45	1–5	1.6–3.3	0.75
S&E	61.8	10–90	53.6–70.0	66	20–90	43.1–89	0.51

AOO = age; TTDx = time to diagnosis; MMSE = mini mental state examination; H&Y = Hoehn and Yahr score; S&E = Schwab and England activities of daily living scale.

Table 1. Demographic and illness staging differences [11].

is mounting evidence that genetics is important in the Parkinson's disease but the studies to date have not been large enough to adequately investigate this. The study by Smith and Modi revealed that a third of Black patients had a positive family history compared to 18% of White patients [11]. A third of Black patients had EOPD (**Table 1**).

The studies focusing on African populations are quite outdated. They all report a lower prevalence of Parkinson's disease in Black populations. However, prevalence is a function of time. These populations had a shorter life expectancy and so this may have influenced prevalence rates. As life expectancy of African populations increases, the increase in the aging population may translate into an increased burden of degenerative diseases such as Parkinson's disease.

What appears consistently throughout these studies is that disease onset appears earlier in Black patients. It is possible that this difference has a genetic basis; however, this theory has yet to be examined further.

4. Phenotype of idiopathic Parkinson's disease

When talking about the phenotype of Parkinson's disease, we describe the cardinal symptoms which dominate the clinical symptoms. According to the Queens Square Brain Bank criteria, bradykinesia is the hallmark of Parkinson's disease. Other cardinal features include resting tremor, muscle rigidity, postural instability, and asymmetry of symptoms. Typically, symptoms are mixed, although rigidity or tremor may predominate. Mixed and tremor predominant types are the most frequent presentation. An akinetic-rigid syndrome, Parkinson-plus disorder having been excluded, is a far less common presentation.

Neurologists have long speculated that the clinical characteristics of Parkinson's disease may differ between populations of African and European origin. The classic description of Parkinson's disease is the hallmark of bradykinesia, associated with a combination of an asymmetrical resting tremor and muscle rigidity to varying degrees. In 2016, Mahne and colleagues

conducted a small study of 16 Black patients with Parkinson's disease in Pretoria, South Africa [10]. Assessment of the phenotype of Parkinson's disease among patients was not the primary outcome of the study. In terms of clinical presentation, 32% were tremor-predominant, 55% were mixed, and 14% had an akinetic-rigid presentation.

A study published by Smith and Modi in the same year aimed to determine whether ethnicity and gender have a significant impact on the clinical presentation of idiopathic Parkinson's disease (IPD) in a patient population in Johannesburg, South Africa [11]. Until then, there had been no notable studies exploring possible differences in disease phenotype between Black and White patients. Of 146 patients with Parkinson's disease screened, 50 patients of different ethnic groups met the inclusion criteria and participated in the study. Seventy percent were Black African, 22% were of European descent, 6% were of Indian descent, and 2% had mixed ancestry. The mean age of the participants was 63 years old (range 36–83).

The study was conducted in a tertiary hospital, which served a predominantly indigent demographic. As a result, the investigators could not draw conclusions on the differences in cognitive impairment, or prevalence of Parkinson's disease in this population. When comparing the different gender and ethnic groups, the study highlighted specific patterns with regards to differences in phenotypes. The chief differences identified were in age of onset, pattern of rigidity (axial or appendicular), posture, and tremor.

The majority of patients in the study population had the classic presentation of Parkinson's disease. This was defined as a syndrome of late onset with an asymmetrical resting tremor, stooped posture, appendicular rigidity, and bradykinesia. This included 91% of White and 71% of Black patients. However, a subset of patients, particularly Black patients, showed some deviations from the classic phenotype.

Of note, Black patients were more likely to have axial (80%) rather than appendicular rigidity (54%) compared to White patients (45 and 90%, respectively.) They were also more likely to have an erect posture (67%). These two findings were statistically significant (p-values = 0.033 and 0.039, respectively). Furthermore, almost a third of Black patients had an akinetic-rigid presentation. This was particularly prevalent in Black males (54%) (**Table 2**).

	Black	**White**
Mean AAO	56.6	60.7
%EOPD	31	18
%Cognitive impairment	74	18
%Akinetic-rigid syndrome	29	9
%Classic IPD	71	91

AOO = age of onset; EOPD = early onset Parkinson's disease.

Table 2. Chief clinical differences found in this study [11].

Several differences were also noted in presentation between the two gender groups. There was a slight female preponderance of 56%, contrary to the male preponderance described in literature. The clinical phenotype between the two groups was similar except for two noticeable differences. Firstly, axial rigidity was more prevalent in males (96%) compared to females (64%). Secondly, resting tremor was much more frequent in females (94%) compared to males (59%). This was statistically significant (p-value = 0.01). The mean age of onset (AOO) was similar in male and female participants in both racial groups.

The phenotype of Parkinson's disease in the majority of the study population was of the classic type. A subset of Black patients (one third) presented with an akinetic-rigid syndrome. The results of the study showed clear trends in the differences between ethnic and gender groups; however, they were not all statistically significant. This is possibly due to the small sample size and hospital complex bias. A larger sample size and community study is needed to confirm these findings.

5. Cognitive impairment

The 2016 Mahne study showed that out of the 16 patients, 40% had a normal cognition, 40% had minimal cognitive impairment, and 20% had dementia. Cognitive impairment was associated with a higher rigidity score UPDRS. Smith's Johannesburg study showed that cognitive impairment was much more common in Black patients than in White patients. There was a higher incidence of cognitive impairment in Black patients. It is important to note that although all participants had a sufficient level of education to complete the Mini Mental State Examination (MMSE), there may have been some bias because of differences in the quality of education, a legacy of the country's history of racial inequality. It is important to note that the MMSE has a culture bias and is not specific for features of a subcortical dementia, which is found in IPD. However, it is a good screening tool and is easily reproducible. The study showed that 75% of Black patients showing an MMSE score of less than 25 compared to 18% of White patients.

6. Conclusion

Parkinson's disease appears to be much less prevalent in African populations than Caucasian populations. However, it is important to note that a true and widespread prevalence study of Parkinson's disease in Africa has yet to be conducted. Although the classical presentation of PD is still the most common, the akinetic-rigid phenotype can be found in up to one-third of African patient. Patients of African origin have a disease onset much earlier than their Northern Hemisphere counterparts as well. There are currently genetic studies underway that will hopefully shed light on these differences in time.

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Chapter 3

Effects of Genetic Variability in Dopaminergic Pathway on Treatment Response in Parkinson's Disease

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.75051

Abstract

Parkinson's disease (PD) is a chronic progressive neurodegenerative brain disorder presenting with motor signs and symptoms, such as akinesia, rest tremor, rigidity, and later in disease progression postural instability. However, nonmotor symptoms may harm patients' quality of life even more than the motor ones. The etiopathogenesis is not clear yet. PD may develop due to a combination of genetic and environmental factors. It is treated symptomatically with dopaminergic drugs. The gold standard of PD management is L-Dopa, however also other drugs are frequently used, such as dopamine agonists, MAOB inhibitors, COMT inhibitors, and occasionally amantadine and anticholinergic drugs. Many patients experience several adverse events of L-Dopa treatment, such as different motor complications. Furthermore, nonmotor adverse events of dopaminergic treatment may occur. The efficacy of drugs varies between patients as well. Several polymorphic genes have already been associated with treatment outcome in PD, such as metabolic enzymes, transport and receptor genes, and might serve as treatment outcome prediction factors. As gene-environment interactions were also shown to contribute to PD development, they might also be able to predict treatment response. Such genetic biomarkers could be helpful in personalized care of PD patients to prevent adverse events and inefficacy of a certain drug.

Keywords: Parkinson's disease, pharmacogenetics, genetic polymorphisms, personalized medicine, L-Dopa, dopaminergic treatment

1. Introduction

Parkinson's disease (PD) is a chronic progressive brain disorder. It is the second most common neurodegenerative disorder after Alzheimer's disease [1]. The exact etiopathogenesis is not clear yet, although it may develop due to various genetic and environmental factors. Two main

pathological hallmarks are indicative of PD: intraneuronal inclusions containing α-synuclein aggregates and neurodegeneration of dopaminergic neurons projecting from substantia nigra (SN) to striatum. Several motor symptoms occur as a result of striatal dopaminergic deficiency: akinesia, rest tremor, rigidity, and in later stages also postural instability with gait disorder [2, 3]. Other motor symptoms encompass hypomimia, micrographia, dysarthria, dysphagia, and others [4]. Furthermore, patients are also affected by nonmotor symptoms. The most common are depression, anxiety, cognitive decline, REM-sleep behavior disorders, constipation, sialorrhoea, and hyposmia. Few of them are present already in the prodromal phase, which may last up to 20 years before the clinical diagnosis is made [2, 3, 5–7].

The underlying molecular pathogenesis of PD encompasses defects in different cellular pathways, such as protein aggregation, protein and membrane trafficking, lysosomal autophagy, immune response, neurodevelopment, neuron cell differentiation and survival, mitochondrial homeostasis, and others [8]. Genetic defects in key genes of these pathways may contribute to the molecular pathogenesis of PD [9].

Clinical diagnosis is normally established by a clinical examination, when motor symptoms are already present. At that time, nearly 80% of dopaminergic neurons in the nigrostriatal pathway are irreversibly lost and only symptomatic treatment is available to alleviate the symptoms. PD management is based on the replacement of dopamine. Some symptoms can also be managed by concomitant supportive therapy, depending on the symptom [2–4].

1.1. Dopaminergic pathway

Dopamine is an organic compound of the catecholamine family. It plays several roles especially in the brain and also in the periphery. It acts as a neurotransmitter and is thus responsible for the transmission of either inhibitory or excitatory stimuli to the postsynaptic neuron depending on the type of the binding receptor. Dopaminergic neurons projecting from substantia nigra pars compacta, part of basal ganglia, to the striatum, which constitutes the nigrostriatal pathway, are responsible for motor functions [10, 11].

Dopamine synthesis and degradation, along with dopamine function in the nigrostriatal pathway, is schematically displayed in **Figure 1**. Tyrosine hydroxylase (TH) converts tyrosine to levodopa (L-Dopa), which is then converted to dopamine by dopa decarboxylase (DDC). Dopamine is then transported to a synaptic vesicle via the vesicular monoamine transporter 2 (VMAT2). It is excreted from the presynaptic neuron to the synaptic cleft via exocytosis. Dopamine then binds to dopamine receptors, either on the membrane of postsynaptic or presynaptic neuron. The downstream effect depends on the receptor it binds to. D1-like receptors (DRD1 and DRD5) are excitatory, whereas D2-like receptors are inhibitory (DRD2, DRD3, and DRD4), which depends on the type of secondary messengers. Binding to the presynaptic receptor inhibits dopamine synthesis and continuous release of dopamine to the synaptic cleft. Once dopamine is released from the receptor, it is reuptaken to the presynaptic neuron via the dopamine transporter (DAT), where it gets deactivated or repackaged into the vesicles by VMAT2 for future release. Metabolism of dopamine is managed by two main enzymes, catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO). Furthermore, aldehyde dehydrogenase (AD) also participates in dopamine

http://dx.doi.org/10.5772/intechopen.75051

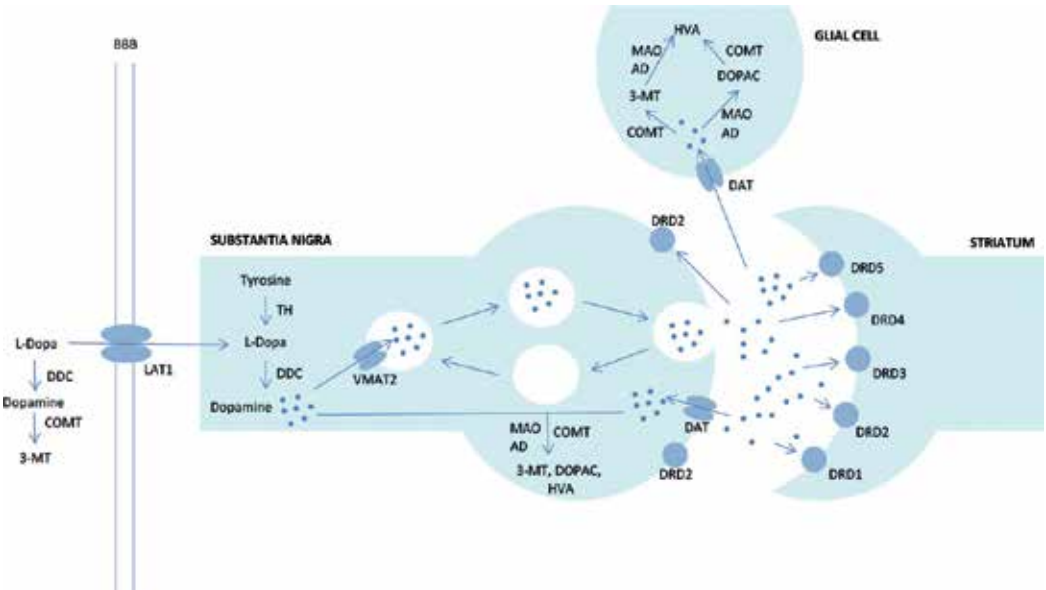

Figure 1. Dopamine synthesis, function, and degradation in the nigrostriatal pathway.

metabolism. COMT introduces a methyl group to the dopamine, whereas MAO catalyzes oxidative deamination. There are two types of the MAO enzyme, MAOA and MAOB. MAOB is more specific for the breakdown of dopamine, whereas MAOA also degrades other catecholamines. Furthermore, AD catalyzes oxidation of aldehydes. As a result of degradation reactions, several different metabolites are produced, such as 3-methoxythyramine (3-MT), 3,4-dihydroxyphenylacetic acid (DOPAC), and homovanillic acid (HVA) as the end metabolite, which gets eliminated in the urine. Degradation of dopamine can either be carried out in the presynaptic neuron after reuptake via DAT or in the glial cells. COMT is predominantly expressed in the glial cells, MAOB in the astrocytes, and MAOA in the catecholaminergic neurons like dopaminergic neurons of SN [12–14].

L-Dopa, which is also the gold standard treatment option in PD, is transported to the brain through the blood-brain barrier (BBB) via large neutral amino acid transporter (LAT1) [15]. L-Dopa can be broken down in the peripheral tissues by COMT and DDC, which might be the source of peripheral adverse events occurring during the treatment. Thus, DDC inhibitors and sometimes also COMT inhibitors are concomitantly administered to shield L-Dopa from degradation. Dopamine itself is not suitable for oral treatment, because it cannot be transported to the brain through the BBB due to its high polarity. Moreover, it is also not an amino acid compound and is thus not a transporter substrate [13].

1.2. Treatment of Parkinson's disease

PD is an incurable disease. Management of PD is based on dopamine replacement and endogenous dopamine enrichment or activation of dopamine receptors. All dopaminergic drugs,

such as MAOB inhibitors, dopamine agonists (DA), L-Dopa, COMT inhibitors, and amantadine, aim to enhance or replenish the dopamine function in the striatum [3].

The least potent drug compounds are MAOB inhibitors, rasagiline, and selegiline. Rasagiline is more broadly used. MAOB inhibitors increase the concentration of dopamine in the synapse and prolong its action by the inhibition of MAOB enzyme. They can either be used as a monotherapy as one of the first prescribed drugs in the early stages of PD or concomitantly with L-Dopa to prolong its action. MAOB inhibitors demonstrate a very small symptomatic benefit, although they might according to some studies have a slight neuroprotective effect. MAOB inhibitors are taken once a day [3, 16–18].

Next line of PD treatment represents DA. DA mimic the dopamine action as they bind to postsynaptic dopamine receptors. Two main types of DA, ergoline and nonergoline derivatives, are available, but usually nonergoline DA are used in clinical practice, such as pramipexole, ropinirole, and rotigotine. They can be used either as monotherapy or in combination with L-Dopa and/or MAOB inhibitors. As their half-life is longer compared to L-Dopa's and the prolonged release forms are available, they can be administered once a day. Rotigotine is available as a transdermal patch. Furthermore, their action is believed to be less pulsatile compared to L-Dopa's, which might be the reason for less motor complications after years of treatment. Nevertheless, their overall symptomatic effect is less pronounced, which means that usually L-Dopa has to be added to therapy in few years after diagnosis. Moreover, apomorphine is a very potent DA, which can be applied subcutaneously, intermittently or as a continuous infusion in advanced disease stages to reduce motor fluctuations [3, 16, 17].

L-Dopa is the gold standard of PD management. L-Dopa crosses the BBB and gets converted to dopamine by DDC in the brain. L-Dopa is always administered in combination with DDC inhibitors, either carbidopa or benserazide. DDC inhibitor is added to prevent L-Dopa conversion to dopamine in the periphery, which could cause several adverse events. L-Dopa alleviates most motor symptoms very effectively, although it poses a high risk for motor complication development. Consequently, many physicians are postponing the L-Dopa prescription to avoid motor complications. Particularly in PD patients younger than 65 years, DA or rasagiline is the common first treatment with L-Dopa being added when the symptomatic effect of DA is not sufficient. However, since the continuous dopaminergic treatment options for advanced PD became available (subcutaneous apomorphine infusion, levodopa/carbidopa intrajejunal gel infusion, and deep brain stimulation), physicians are less hesitant to prescribe L-Dopa early in the disease course. L-Dopa is usually administered in the form of tablets, which are taken a few times daily (3–6 times) to deliver L-Dopa as continuously as possible [3, 13, 16, 17]. Furthermore, COMT inhibitors, especially entacapone, are commonly used concomitantly with L-Dopa when early motor fluctuations (wearing-off phenomena) occur. On the other hand, amantadine may be used to alleviate L-Dopa-induced dyskinesia [16].

Management of PD should be individualized in the scope of options available. Patient's age, symptoms' severity, and cognitive status are considered in the process of choosing the most suitable drug [2, 17].

http://dx.doi.org/10.5772/intechopen.75051

1.3. Adverse events of dopaminergic treatment

Dopaminergic therapy can cause several adverse events (AEs), which can be classified as motor and nonmotor ones.

Several peripheral AEs can occur during PD treatment. The common peripheral AEs are nausea and vomiting, which occur in approximately 15% of PD patients treated with dopaminergic drugs. Nausea and vomiting can be avoided by a very slow titration of a drug dose or by concomitant administration of domperidone at the initiation of treatment. Furthermore, orthostatic hypotension is also common in PD patients as 34% of patients experience this AE after the first dose of a DA. Peripheral edema usually limited to ankles is mostly occurring in DA treatment rather than L-Dopa treatment. It affects 6.4% of patients treated with ropinirole and 15% of patients treated with pramipexole. Risk factors for the development of edema are female sex and cardiovascular comorbidities [19–21].

Central AEs are excessive daytime sleepiness and sleep attacks, hallucinations, and impulse control disorders (ICD). Excessive daytime sleepiness and sleep attacks affect approximately 30% of patients taking dopaminergic medications, especially DA. Sleep attacks are defined as a sudden, irresistible, and overwhelming sleepiness without awareness of falling asleep. Good sleep hygiene is very important in PD patients to prevent daytime sleepiness, so some nonpharmacological interventions can be undertaken to achieve as many hours of sleep during night as possible to avoid this AE. It is important to warn the patients about this possible AE and advise them not to drive a vehicle during DA titration phase. Furthermore, hallucinations in PD are mostly visual. Patients usually see simple and not threatening images of silent animals and people. Although all dopaminergic drugs are associated with this AE, patients taking DA are more likely to be affected. Longer duration of the disease and cognitive impairment are risk factors for the development of visual hallucinations [19–21]. They affect from 25 to 39.8% of PD patients [19]. ICD prevalence rates reports are quite variable and range from 6 to 39%. This AE presents as pathological gambling, hypersexuality, compulsive buying, and binge eating. The AE should be recognized early due to possible severe personal, financial, and socio-familial consequences when it remains unrecognized [19–21].

Motor AEs occur after few months to few years of treatment with L-Dopa and affect almost every PD patient chronically treated with L-Dopa. The time and severity of motor complications vary among patients and cannot be predicted yet. The most common motor complications are motor fluctuations, which first manifest as *wearing-off* of the drug effect before the next dose is administered. Consequently, patient fluctuates between *on* and *off* periods. During the *on* period, motor symptoms are least pronounced, whereas in the *off* period, symptoms re-emerge. Motor fluctuations may occur because of long-lasting pulsatile stimulation of striatal dopamine receptors, and as the disease advances, the ability to store dopamine is diminished and finally lost. Consequently, the patients' clinical picture parallels the blood L-Dopa level. The fluctuations may be managed either by increasing the number of smaller L-Dopa doses and/or by adding the COMT inhibitors, MAOB inhibitors or DA, which may prolong L-Dopa action. Dyskinesia is another type of motor complications. It is usually defined as involuntary and choreatic movements most

often related to the peak dopamine levels (peak-dose dyskinesia). This type of dyskinesia is usually managed by reducing the single L-Dopa doses or by discontinuation of COMT or MAOB inhibitors, but this intervention may prolong the *off* periods. Furthermore, diphasic dyskinesia may occur as plasma L-Dopa levels are rising or falling. It is more bothersome for the patient, with dystonic features and difficult to treat. The same strategies may be used as for the treatment of peak-dose dyskinesia. The third type of dyskinesia occurs in the *off* state, and is usually presented as painful early morning leg dystonia, when the blood L-Dopa level falls low due to long time since the last L-Dopa dose. It can be managed by taking the prolonged release L-Dopa at night or by adding COMT inhibitors, MAOB inhibitors or DA [2, 14, 17, 19–21]. Botulinum toxin injection in the affected muscle is effective too [22]. L-Dopa-induced dyskinesia can also be treated by adding amantadine to the therapy scheme [2, 14, 17, 19–21].

1.4. Treatment efficacy evaluation with the MDS-unified Parkinson's disease rating scale (MDS-UPDRS)

MDS-UPDRS is a four part scale for the evaluation of PD severity and treatment efficacy. Part I evaluates nonmotor aspects of experiences of daily living, Part II motor aspects of experiences of daily living, Part III motor examination, and Part IV motor complications. The first part of Part I and Parts III and IV are evaluated by physicians, whereas the second part of Part I and the whole Part II are self-administered by patients. MDS-UPDRS can be used for different applications, but in some pharmacogenetic studies, where the efficacy of dopaminergic drugs is evaluated in association with genetic factors, the main efficacy criterion is a difference in MDS-UPDRS score over a particular period of time [16, 23–26].

1.5. Genetic factors and treatment response in PD

Genetic characteristics of each person are encoded in the genome. Interindividual differences occur due to changes in DNA in only 1% of the whole sequence. Different variants of the same gene or locus are called alleles. Furthermore, a variant is called a polymorphism when at least two different alleles are present in the population and the less frequent allele is carried by at least 1% of population. The most common type of genetic variation are single nucleotide polymorphisms (SNPs), where one nucleotide is substituted with the other. Furthermore, many other types of polymorphisms can change the DNA sequence, such as deletions, insertions, duplications of nucleotides or longer sequences, microsatellites, changes in variable number of tandem nucleotide repeats (VNTR), and others. These genetic polymorphisms may lead to changes in transcription, translation, and/or function of proteins [27, 28]. These polymorphisms may also influence expression and function of proteins involved in metabolism, transport and effector pathways of drugs, and also structure and function of drug targets. Consequently, polymorphisms may have an effect on drug response in terms of efficacy and occurrence of AEs. Also in PD, this effect has already been shown in several pharmacogenetic studies [29, 30].

The aim of this chapter is to summarize the current knowledge on the effect of different polymorphisms, mostly SNPs, on dopaminergic treatment outcome, especially the occurrence of AEs. The chapter focuses on the polymorphisms within the dopaminergic pathway, but also includes polymorphisms from other pathways, that have already been associated with

treatment response. The rationale behind investigating polymorphisms is that they may serve as the possible predictive biomarkers of treatment response in PD patients and could therefore support personalized treatment approaches. Furthermore, this chapter also discusses gene-environment interactions already investigated in PD.

2. Genetic variability in dopaminergic receptor genes affecting response to PD treatment

Dopaminergic receptors reside in the membrane of postsynaptic neurons in striatum. There are five types of dopaminergic receptors, divided into two groups—type-1 and type-2. Dopaminergic receptors are coded by *DRD1–5* genes [14]. At least 11 pharmacogenetic studies (**Table 1**) have already been performed searching for associations between different *DRD* gene variants and AEs or efficacy and have found positive results [23, 31–40].

Genes	Variants	p-Value	No. of PD patients	Outcome	Reference
DRD1	rs4867798 c.*863A>G	0.0054	91	Impulse control disorder	[31]
	rs4532 c.-48G>A	0.0024			
DRD2/ANKK1	rs1800497 c.2170G>A p.Glu724Lys	0.0009	274	Sleep attacks	[32]
		0.0044	91	Impulse control disorder	[31]
	-141CIns/Del	0.007	199	Dyskinesia	[33]
	rs2283265 c.724-353G>T				
	rs1076560 c.811-83G>T				
	rs6277 c.957C>T p.Pro319=				
	rs1800497 c.2170G>A p.Glu724Lys				
	rs2734849 c.1469A>G p.His490Pro				
DRD2	(CA)n-STR	0.005	215	Dyskinesia	[34]
		0.04 (14 allele) 0.003 (14/15 genotype)	92	Dyskinesia	[35]
	rs1799732 c.-486_-485insC	0.027	217	Nausea and vomiting	[36]
DRD3		0.0094	404	Impulse control disorder	[37]

Genes	Variants	p-Value	No. of PD patients	Outcome	Reference
	rs6280 c.25G>A p.Gly9Ser	0.024	30	Therapeutic efficacy	[23]
		0.041	170	Impulse control disorder	[38]
		0.022	217	Nausea and vomiting	[36]
		0.001	168	Dose of dopamine agonist	[39]
DRD4	48-bp VNTR	<0.0001	204	Sleep attacks	[40]

Table 1. Genetic polymorphisms in dopaminergic receptor genes associated with dopaminergic treatment outcome in patients with PD.

DRD1 was reported to be associated with L-Dopa-induced dyskinesia. Carriers of the rs4867798 C allele and rs4532 T allele were more prone to develop this AE [31]. Association of *DRD2* variants with drug response was shown in at least six studies [31–36]. *DRD2* (CA)n-STR (intronic short tandem repeat with four common alleles—13, 14, 15, and 16 CA repeats) was checked for association with dyskinesia after L-Dopa treatment. Results showed association of allele with 14 repeats and 14 repeats/15 repeats genotype as associated with earlier development of dyskinesia [35]. The same variant was also evaluated in the study performed by Zappia et al. Male carriers of the 13 and/or 14 repeat alleles had a decreased risk for developing dyskinesia, whereas in females the association was not confirmed [34]. Furthermore, *DRD2* haplotype of six variants (-141CIns/Del, rs2283265, rs1076560, rs6277, rs1800497, and rs2734849) was checked for association with dyskinesia. Carriers of the TTCTA haplotype were more likely to develop L-Dopa-induced dyskinesia [33]. Association of *DRD2* rs1800497 with ICDs was found in a study performed by Zainal Abidin et al. T allele significantly increased risk for ICD [31]. This SNP was also associated with sleep attacks, namely G allele increased chances of this AE [32]. Moreover, *DRD2* rs1799732 Ins/Ins genotype was associated with gastrointestinal AEs (nausea and vomiting) after L-Dopa therapy [36]. Association of *DRD3* variants with drug outcome in PD was shown in at least five pharmacogenetic studies [23, 36–39]. *DRD3* rs6280 AA genotype (Ser/Ser) was shown to be associated with increased risk for developing ICDs and gastrointestinal AE [36, 37]. Furthermore, the same genotype was also associated with higher response rate in treatment with pramipexole [23]. Another study showed that heterozygous genotype carriers of this were more prone to develop ICDs [38]. Lastly, Gly/Gly genotype of rs6280 was associated with higher doses of DA needed to manage PD [39]. *DRD4* was also already reported to be associated with AE in dopaminergic treatment. Sleep attacks were more likely to develop in carriers of the short allele of the 48-bp VNTR in exon 3 of the gene [40].

3. Genetic variability in transporter genes affecting response to PD treatment

Most frequently studied transporter gene in pharmacogenetic of PD is *SLC6A3* encoding DAT. DAT is located in the membrane of presynaptic dopaminergic neurons and of glial cells almost exclusively in striatum. It pumps dopamine from the synaptic cleft back to the presynaptic neuron or into the glial cell. Consequently, it ends the action of dopamine in

Genes	Variants	p-Value	No. of PD patients	Outcome	Reference
SLC6A3	rs28363170 3′-UTR 40 bp VNTR	0.006	183	Psychosis and dyskinesia	[41]
	rs2652511 c.-972T>C	0.02	196	Visual hallucinations and levodopa equivalent dose	[42]
	rs28363170 3′-UTR 40 bp VNTR	0.01			
	rs393795 c.653+4065C>A	4.1E−5	352	Dyskinesia	[43]
	rs3836790 (VNTR in intron 8–5/6 repeat)	<0.0001	61	Motor response to acute L-Dopa challenge	[44]
SLC22A1	rs622342 c.1386-2964C>A	0.017	99	Levodopa dose	[45]

Table 2. Genetic polymorphisms in dopaminergic transporter genes associated with dopaminergic treatment outcome in patients with PD.

the synaptic cleft. At least four studies (**Table 2**) have already shown association of polymorphisms in *SLC6A3* with response to dopaminergic treatment [41–44]. First, a study by Kaiser et al. showed association of the nine copy allele 40-bp VNTR of the DAT with the occurrence of dyskinesia and psychosis after L-Dopa treatment [41]. Furthermore, this variant showed association with L-Dopa equivalent dose (LED) needed for proper disease management, where nine repeat allele of the DAT 3′-UTR VNTR was associated with lower LED [42]. In the same study, *SLC6A3* rs2652511 C allele was shown to be associated with visual hallucinations [42]. Moreover, C allele of the rs393795 in *SLC6A3* was recognized as one of the factors that extend the time to dyskinesia occurrence in L-Dopa treatment [43]. After an acute L-Dopa challenge, patients with six repeat/six repeat genotype of the VNTR in intron 8 responded better [44].

Organic cation transporters (OCT) are involved in the absorption, distribution, and elimination of a wide variety of compounds. Pramipexole and amantadine are substrates for OCT1 and OCT2. L-Dopa is also transported by one of the OCTs, but the subtype has not been determined yet. Becker et al. evaluated the association between the rs622342 and the dose of dopaminergic drugs needed for proper disease management (**Table 2**). Between the first and fifth L-Dopa prescription, for each minor rs622342 C allele, the prescribed doses were 0.34 defined daily dose higher (DDD), where DDD is a standardized dosing measure representing the recommended daily dose for the main indication in an adult [45].

4. Genetic variability in dopamine metabolic pathway genes affecting response to PD treatment

Three enzymes in the metabolic pathway of dopamine, COMT, MAO-B, and DDC, have already been associated with the response to dopaminergic treatment in PD (**Table 3**).

Genes	Variants	p-Value	No. of PD patients	Outcome	Reference
COMT	rs4680 c.472G>A p.Val158Met	0.047	121	Wearing-*off* phenomenon	[46]
		0.045		Dyskinesia	
		0.18 (NS)	95	L-Dopa dose	[49]
		0.004	219	Dyskinesia	[50]
		0.049 (GG) 0.031 (G allele)	1087	Wearing-*off* phenomenon	[47]
		<0.001	259	Wearing-*off* phenomenon	[48]
	rs6269 c.-98A>G	<0.05	322	L-Dopa dose and dyskinesia	[51]
	rs4633 c.186C>T p.His62=				
	rs4818 c.408C>G p.Leu136=				
	rs4680 c.472G>A p.Val158Met				
MAO-B	rs1799836 c.1300-36A>G	0.018	1087	Dyskinesia	[47]
DDC	rs921451 c.-29+9697A>G	0.0097	33	Motor response to acute L-Dopa challenge	[26]
	rs3837091 c.-61_-58delAGAG				

NS, not significant.

Table 3. Genetic polymorphisms in dopamine metabolic genes associated with dopaminergic treatment outcome in patients with PD.

Polymorphism rs4680 has been the most studied SNP in the *COMT* gene in association with treatment outcome by now. The substitution of nucleotides in the SNP results in the switch of valine to methionine (p.Val158Met). This substitution causes lower activity of the enzyme. In the majority of the studies, this switch was associated with motor complications of L-Dopa treatment. Watanabe et al. showed that homozygosity for the low-activity allele (AA genotype) increased chances for wearing-*off* phenomenon ($p = 0.047$) and dyskinesia ($p = 0.045$) [46]. On the contrary, a later study found association of the GG genotype with wearing-*off* phenomenon ($p = 0.049$ for the GG genotype and 0.031 for the G allele) [47]. The same results were also found in the study by Wu et al. [48]. In another study, the same SNP was checked for association with the dose of L-Dopa after the first 5 years of treatment. The association was not significant, but the frequency of homozygotes for the AA genotype was higher in a group with lower doses of L-Dopa (500 mg/24 h) [49]. The same genotype was also associated with the development of dyskinesia with evidence of a dose-response effect [50]. One of the studies

also checked the association between the most common COMT haplotypes of four SNPs—rs6269, rs4633, rs4818, and rs4680. The enzyme activity differs between haplotypes: low activity—ACCG, medium activity—ATCA, and high activity—GCGG. The L-Dopa dose increased with the activity of the enzyme (low < medium < high). Doses prescribed to low-activity haplotype carriers were significantly higher in comparison to noncarriers. No association was found for dyskinesia [51].

Devos et al. investigated *DDC* variants for the association with response after acute L-Dopa challenge. Response to L-Dopa was evaluated by the area under the curve for the change in the UPDRS Part III score ($AUC_{\Delta UPDRS}$) 4 h after L-Dopa administration relative to baseline. The $AUC_{\Delta UPDRS}$ was significantly lower in rs921451 CC or CT genotypes than in TT genotype. Furthermore, $AUC_{\Delta UPDRS}$ was also significantly lower in rs3837091 Del/Del or AGAG/Del genotypes than in the AGAG/AGAG genotype [26].

MAO-B is also important in dopamine metabolism and its variants affect drug response. Carriers of the heterozygous genotype at the *MAO-B* rs3837091 were found to be more prone to develop dyskinesia [47].

5. Genetic variability in other genes affecting response to PD treatment

Genetic variability in several other pathways and its influence on drug response in PD was also investigated in several studies and some statistically significant associations have been found (**Table 4**).

At least four pharmacogenetic studies pointed out association of nondopaminergic genes with the occurrence of dyskinesia [35, 52–54]. Higher chance for developing L-Dopa-induced dyskinesia was described in carriers of the following genotypes or alleles within different systems: opioid system—*OPRM1* rs1799971 G allele; neuroprotection system—*BDNF* rs6265 A allele; glutamate system—*GRIN2A* rs7192557 GG genotype, rs8057394 CC genotype; adenosine pathway—*ADORA2A* rs2298383 TT and CT genotypes, rs3761422 CC, and CT genotypes [35, 52–54]. Psychosis as an AE of DA or L-Dopa was already associated with *APOE, ACE, HOMER1*. APOE ε4 allele increased risk for the earlier development of psychosis [55]. *ACE* deletion/insertion (D/I) of a 287-base pair Alu repeat sequence in the intron 16 was associated with psychosis after L-Dopa treatment, namely I/I genotype increased risk for development of the AE [56]. Furthermore, allele A of the *HOMER1* rs4704559 increased risk for development of psychosis, especially hallucinations [57]. Another AE occurring in dopaminergic treatment are sleep attacks. According to Rissling et al. *HCRT* rs760282 T allele increased risk for developing this AE, where TT genotype carriers were even more susceptible to it [58]. *GRIN2B* and ICDs are another association of the glutamate system with AE of dopaminergic treatment. *GRIN2B* rs7301328 CC genotype increased risk for at least one of the types of ICDs [37]. The same finding was reported by Zainal Abidin et al. [31]. Also, *HTR2A* receptor in the serotonin system was according to Lee et al. associated with ICD. The T allele, which is presumably associated with higher expression of the receptor, increased risk for developing ICDs in the lower-L-Dopa-equivalent dose group [59]. *SV2C,* which participates in the process of

Gene	Variants	p-Value	No. of PD patients	Outcome	Reference
HCRT	rs760282 c.-909T>C	0.024 (TC) 0.018 (TT)	264	Sleep attacks	[58]
APOE	*e4* allele	<0.05	87	Psychosis	[55]
OPRM1	rs1799971 c.118A>G p.Asn40Asp	0.05	92	Dyskinesia	[35]
ACE	A deletion/insertion (I/D) of a 287-base pair Alu repeat sequence in the intron 16	0.012	251	Psychosis	[56]
HOMER1	rs4704559 g.78812909A>G	0.004	131	Psychosis	[57]
BDNF	rs6265 c.196G>A p.Val66Met	0.001	315	Dyskinesia	[52]
GRIN2B	rs7301328 c.366C>G p.Pro122=	0.0087	404	Impulse control disorders	[37]
		0.0097	91	Impulse control disorders	[31]
GRIN2A	rs7192557 c.415-91061C>T	0.0062	101	Dyskinesia	[53]
	rs8057394 c.415-83080G>C	0.0033			
ADORA2A	rs2298383 c.-275+1797C>T	0.023 (TT) 0.039 (CT)	208	Dyskinesia	[54]
	rs3761422 c.-274-2427T>C	0.017 (CC) 0.012 (CT)			
HTR2A	rs6313 c.102C>T p.Ser34=	0.011	404	Impulse control disorders	[59]
SV2C	rs30196 c.-1888G>T	0.024	224	L-Dopa dose	[60]

Table 4. Genetic polymorphisms in other genes associated with dopaminergic treatment outcome in patients with PD.

dopamine storage in vesicles, was associated with L-Dopa dose. The presence of each rs30196 C allele reduced the average dose of L-Dopa for approximately 76 mg per day [60].

6. The role of gene-environment interactions in PD

So far, mostly genetic factors have been investigated as potential modifiers of drug response. However, drug response can also be influenced either directly or indirectly by environmental factors. Several environmental factors have already been associated with PD risk, among them: coffee and alcohol consumption and cigarette smoking are reducing and pesticide

exposure and well water drinking are increasing the risk. Several single locus and genome wide studies evaluating gene-environment interactions have already been performed in PD and these interactions should also be assessed in association with the treatment outcome (**Table 5**) [2, 61, 62].

A genome-wide gene-environment study found association between *GRIN2A* rs4998386 in combination with coffee consumption and PD risk. Light-coffee drinkers were defined as people with ccy (cups per day multiplied by the number of years of coffee consumption) less than median ccy (three datasets with different medians: 67.5, 70.0, and 74.0) and heavy-coffee drinkers as people with ccy more than median ccy. The *GRIN2A* association was present in heavy-coffee drinkers, but not in light-coffee drinkers. T allele decreased risk for PD in comparison to CC genotype in heavy-coffee drinkers. Compared to light-coffee drinkers CC genotype carriers, heavy-coffee drinkers with CC and CT genotype had lower risk for PD [63]. Furthermore, Gao et al. investigated interaction of both smoking and coffee drinking with genetic factors and their combined effect on risk for PD. *SLC2A13* rs2896905 was recognized as an important risk modifier. Each A allele was associated with a 35% higher PD risk among never smokers with low caffeine intake, but with a 32% lower risk among smokers with high caffeine intake [64]. *SV2C*, which was

Gene	Variants	p-Value	Number of participants	Outcome	Reference
SV2C	rs30196 c.-1888G>T rs10214163 c.-101-133065C>T	1E-10	1600 cases 1506 controls	PD risk and smoking	[65]
SLC12A3	rs2896905 c.556+5639C>T	0.0008	584 cases 1571 controls	PD risk and smoking and coffee drinking	[64]
ERCC6L2	rs67383717 g.98626548C>A	2.4E-6	443 cases 443 sibling controls	PD risk and pesticide exposure	[68]
BST1	rs11724635 c.852-575C>A	0.024 (AC) 0.008 (CC)	468 cases 487 controls	PD risk and well water drinking	[66]
SNCA	rs3775423 c.307-7063G>A	<0.05	1098 cases 1098 controls	PD risk in combination with pesticide exposure and coffee and alcohol consumption	[67]
MAPT	rs4792891 c.-18+1448T>G				
	H1/H2 haplotype				
	rs16940806 c.*2289G>A				
	rs2435211 c.1127-1162C>T				
GRIN2A	rs4998386 c.415-38137G>A	6E−7	Initial phase: 1458 cases 931 controls Replication phase: 1014 cases 1917 controls	PD risk and coffee drinking	[63]

Table 5. Results of studies on gene–environment interactions in PD.

already associated with drug response in one of the pharmacogenetic studies, showed association with PD risk in combination with smoking. Two SNPs rs30196 and rs10214163 protected from PD risk, when people carried both wild type alleles (CC and TT, respectively). The risk increased with number of polymorphic alleles [65]. A single locus study aimed to look for association between the combined effect of well water drinking and *BST1* rs11724635 and PD. The results show that polymorphic rs11724635 AC and CC genotypes combined with well water drinking increase risk for PD [66]. Another study investigated gene-environment interactions for *SNCA* and *MAPT* with multiple environmental factors. Five interactions were associated with PD risk: pesticides × *SNCA* rs3775423 or *MAPT* rs4792891, coffee drinking × *MAPT* H1/H2 haplotype or *MAPT* rs16940806, and alcohol drinking × *MAPT* rs2435211. Unfortunately, no interaction remained significant after Bonferroni correction [67]. Lately, a genome-wide gene-interaction study of pesticide exposure and PD risk was performed. No results remained significant after genome-wide correction for multiple testing. Top signal of the *ERCC6L2* gene suggested that this gene may modify the effect of pesticide exposure on PD risk [68].

7. Future perspectives

PD is a complex and heterogeneous syndrome, which presents with different signs and symptoms in different patients and progresses with different rates. The current treatment approach to individual patients varies depending on the patient's age, disease duration, disease severity, and cognitive state. The treatment regime is then adjusted according to treatment's efficacy, the disease progression and in regard to AEs. We have searched the current literature to compile a comprehensive review of today's knowledge on genetic variants that may influence the outcome of dopaminergic treatment in PD. At least 35 pharmacogenetic studies have already been published in PD. Several genetic factors potentially predictive of treatment outcome have already been found, although some of the studies show conflicting results regarding the same genetic factors. This may be largely due to the small size of the study cohorts, since many studies included less than 100 patients. The largest study was performed on a cohort of 1087 patients.

Pharmacogenetic studies in PD mostly look at the treatment outcome of dopaminergic drugs in general, rarely they focus on a particular drug as patients are usually treated with the combination of treatments. Furthermore, most of the cohorts included patients with different symptomatology, which may also reflect differences in pathogenesis of PD in these patients, consistent with reports that different cellular defects contribute to development of PD or are even causative of PD [8]. As cohorts in pharmacogenetic studies are so heterogeneous, significant factors that may predict treatment outcome may be overlooked, because they might be relevant only for one particular subgroup of PD patients but not for the others. If we could stratify PD patients according to cellular pathways that may be defective in each subgroup, predictive genetic factors could be found more easily.

The future studies should also expand the range of polymorphisms investigated as potential predictive biomarkers. So far, researchers have mostly focused on dopamine receptor genes, transporter genes, dopamine metabolic genes, and few genes in other pathways, but there

are plenty of genes that warrant further analysis. For example, genes involved in the pathways of inflammation (*IL-1*, *IL-6*, *TNFα*, and *IFNγ*), oxidative stress (*CAT*, *SOD*, and *GPX*), neurodevelopment (*BDNF*, *GDNF*, and *NOTCH*), mitochondrial and lysosomal function, and also genes significant in gene-environment interaction studies (*SLC12A3*, *ERCC6L2*, *BST1*, *SNCA*, and *MAPT*). Furthermore, some of the genes that increased PD risk in genome-wide association studies could also influence treatment outcome (*GBA*, *SYT11*, *INPP5F*, *SNCA*, *MAPT*, *TMEM175*, *GAK*, *DGKQ*, *STK39*, and *HLA-DQB*).

The validated pharmacogenetic biomarkers would enable physicians to stratify PD patients according to their genetic characteristics and not only by their phenotype. Stratification would allow a more targeted pharmacotherapy and a more individualized approach to treatment. Pharmacogenetic factors could also be supported with clinical data. Algorithms encompassing both aspects, clinical and genetic, could be constructed to enable physicians to choose the most suitable treatment strategy for each patient at the particular stage of the disease. If such algorithms are constructed, AE and treatment inefficacy could be at least minimized if not avoided. As PD pharmacotherapy is usually very complex and drugs are taken many times daily patients' compliance may be expected to improve with better treatment outcome, as well as their quality of life.

8. Conclusions

Personalized medicine has been evolving rapidly in the recent years, but the reliable biomarkers of treatment outcome are not validated yet. The ultimate goal of personalized medicine is to approach every patient individually and provide the best care possible for each individual patient. In this chapter, we summarized the current knowledge on genetic predictors of response to dopaminergic treatment in PD patients. Additionally, we looked into gene-environment interaction studies to find potential biomarkers that should be further evaluated in pharmacogenetic studies. Many studies have already been performed, but the cohorts were small and heterogeneous. To be able to validate and translate these findings into clinical practice, more targeted studies with larger cohorts and better characterized patients should be conducted. However, some promising candidates have already been identified and could be used in clinical practice after validation in independent cohorts.

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Section 2

Parkinson's Disease Therapeutics: Challenges and New Developments

Chapter 4

Non-Invasive Neuromodulation Therapies for Parkinson's Disease

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.75052

Abstract

Noninvasive brain stimulation (NIBS) technologies have been applied to study brain physiology and, more recently, have been recognized for their therapeutic potential as an adjunctive treatment for various neurologic and psychiatric disorders. Transcranial magnetic stimulation (TMS) and transcranial electric stimulation (tES) are two of the most studied NIBS modalities in Parkinson's disease. They are non-systemic and relatively safe. Most therapeutic trials have been conducted to ameliorate motor symptoms of Parkinson's disease (PD) with overall positive results using various stimulation modalities and methods. Notwithstanding significant results, evidence has not yet been compelling mainly due to small-size studies, lack of standardization of methodologies and other study design limitations. NIBS hold promise for treatment of PD symptoms and PD related complications. Large, well designed clinical trials are needed to corroborate these positive findings and inform its durability and the overall clinical relevance for the treatment of PD.

Keywords: neuromodulation, brain stimulation, electric stimulation, TMS, direct current, therapy, Parkinson's disease

1. Introduction

Parkinson's disease (PD) affects as many as 1.5 million people in the United States, with about 60,000 additional patients newly diagnosed each year. PD is a chronic, progressive syndrome in which a large number of dopaminergic neurons located within the basal ganglia circuitry degenerate. This dopamine depletion contributes to clinical motor symptomatology, including bradykinesia, tremor, rigidity, postural instability and gait dysfunction. Despite currently

available treatments, PD symptoms progress along with cortical dysfunction, leading to cumulative disability. The pharmacotherapy of PD is based on the restoration of dopamine levels through the administration of its precursor, levodopa (L-DOPA). Less powerful therapeutic strategies involve the direct stimulation of post-synaptic dopaminergic receptors through dopamine-agonist compounds or the inhibition of dopamine breakdown through catabolic inhibitors. A good control of symptoms is commonly obtained, leading to a good functional recovery, as well as to a general betterment of quality of life. Nonetheless, the results are maintained for a limited period, and, after a few years, certain complications related to the medication may arise, thus limiting the tolerability and the effectiveness of the treatment. At this point, doses are often limited by side-effects such as drowsiness, orthostasis, nausea, confusion, hallucinations, and the emergence of motor complications like fluctuations and dyskinesias. Furthermore, some symptoms known to be poorly responsive to available medications, such as freezing of gait, balance impairment and postural abnormalities, tend to emerge as the disease progresses. In the last decade, different therapeutic strategies have been developed in the effort to address the advanced stage of the disease, typically characterized by a progressive functional decline and decrease in quality of life with an unsatisfactory response to conventional pharmacological treatments. These "advanced strategies" show a variable profile of effectiveness and invasiveness. A recently introduced therapy is the duodenal administration of a gel formulation of L-DOPA (Duodopa), which is continuously released though a duodenal tube connected to a portable pump through a percutaneous endoscopic gastrostomy. This device permits a continuous delivery of the drug, with a stable kinetics, resulting in a significant reduction of the OFF-time and a marked simplification of the oral therapy. There are also more invasive surgical options that could offer symptomatic benefits. Deep brain stimulation (DBS) is the most commonly performed surgical treatment for Parkinson's, but it is not recommended for all patients. DBS has been demonstrated to be effective in remodulating the pathological activity of the basal ganglia motor circuit by acting on specific nuclei, including the subthalamic nucleus, the *globus pallidus* interna and the thalamus. This technique involves the implantation of pacing devices providing a continuous high frequency stimulation of the targeted area. DBS can ease some PD symptoms and motor fluctuations, but it does not change the underlying course of disease. Currently, there are no disease-modifying therapies available. Disease progression and disability eventually require a multidisciplinary approach involving physical therapy, social/occupational therapy, psychotherapy, etc. Alternative treatments able to maintain or reconsolidate function and quality of life are needed. Non-invasive brain stimulation (NIBS) techniques are potential adjunct therapies for PD. NIBS techniques do not require surgical intervention and are performed in outpatient settings. The practicality and safety of NIBS result in an important alternative therapy to maintain physical and/or cognitive function or promote functional recovery in PD patients.

NIBS is an area of rapid growth in neuroscience. The term "non-invasive brain stimulation" encompasses different modalities of intervention involving the administration of energy to modify the bioelectrical state of neuronal cells and influence brain regional activity. There is some controversy surrounding the name; some have suggested that the term "non-invasive" misrepresents both the possibility of side effects from the stimulation, and the longer-term effects (both adverse and desirable) that may result from brain stimulation [1]. The "non-invasive" denomination, as used in this review, is derived from the fact that the intervention does not require the insertion of instruments through the skin or into a body cavity.

http://dx.doi.org/10.5772/intechopen.75052

The different sub-modalities of NIBS are named based upon how energy is physically delivered to the brain. In transcranial magnetic stimulation (TMS), transient rapid changing magnetic fields are utilized to induce secondary electric currents in the underlying cortical surface, which, in turn, trigger neuronal action potentials [2]. By contrast, in transcranial electric stimulation (tES), a weak electrical current is directly applied to the scalp to modulate neuronal membrane potentials without directly inducing synchronized neuronal discharge [3]. These different modalities of NIBS have shown a clear capacity to modify cortical excitability and potentially harness neuroplasticity for therapeutic applications, and they will be revised separately. The substantially safe, reproducible and non-invasive nature of NIBS makes these techniques of appealing interest for the study and treatment of various neurological and psychiatric disorders including PD. NIBS has proven efficacy in depression and chronic pain. NIBS in Parkinson's disease have led to numerous publications and variable results that we intend to summarize and review with a focus in research clinical trials (RCT). The chapter will be a narrative review describing the latest advancements in utilizing transcranial magnetic stimulation (TMS) and transcranial electric stimulation (tES). The proposed mechanisms of neuromodulation, its safety, therapeutic results and challenges will also be reviewed.

2. Mechanisms of action of non-invasive brain stimulation

The biological effects of NIBS are essentially determined by two types of factors: extrinsic (related to the intervention) and intrinsic (related to the stimulated subject). On one hand, extrinsic factors are related to the amount of energy and to the pattern of current flow delivered to the brain. These include specific parameters that can be actively controlled by the operator, such as current intensity, stimulation frequency, number of pulses, number of sessions, coil design, electrode montage, etc. However, for the same dose of energy delivered, different intrinsic factors inherent to the stimulated subject contribute to the individual's biological outcome. For instance, the subject's pharmacological profile can affect the brain's activation state and connectivity by modulating neuronal propensity to fire and undergo plastic phenomena. In patients with Parkinson's disease (PD), this is particularly noteworthy, as changes in cortical excitability and neuroplasticity are critically influenced by dopamine bioavailability, and the institution of a dopaminergic therapy can influence the subsequent neurophysiologic and behavioral effects of stimulation [4].

2.1. Motor cortex transcranial magnetic stimulation (TMS)

TMS is a focal modality of NIBS where an intermittent, high intensity, electrical current of brief duration is generated through a capacitor to induce transient magnetic fields spreading from the coil to the underlying surface. TMS has an FDA cleared indication for the treatment of medication refractory depression. As described by Michael Faraday's electromagnetic principle, the temporal variation of such magnetic fields—namely their exchange rate—is associated with the induction of secondary electrical currents. These currents are capable of triggering neuronal action potentials; the volume of the stimulated area roughly falls into that of a golf ball, and the transfer of energy is maximal with parallel orientation of conductors. Due to the

anatomical structure of the cortical layers, most of the neurons whose firing can be manipulated through TMS are parallel to the scalp and, as such, are mainly represented by interneurons. These cells can trans-synaptically modify the activity of interconnected pyramidal cells through indirect descendent volleys known as "I-waves" [5]. Descending volleys originating from the motor cortex (M1) can be recorded with electrodes from the peripheral muscle and the recordings are regarded as motor evoked potentials (MEPs). When TMS is delivered repetitively in trains of sufficient intensity and duration (e.g. 10–30 minutes), it is able to exert modulatory effects as evidenced by changes in MEPs amplitude, with an effect that outlasts each stimulation train. Therefore, the neurophysiological effects of trains of repetitive TMS (rTMS) can be quantified in light of some indirect neurophysiologic parameters, which are regarded as markers of cortical excitability. In healthy subjects, different stimulation frequencies are associated with opposite changes in local cortical excitability. More specifically, repetitive TMS (rTMS) at a frequency of one pulse/second (1 Hz) is associated with "inhibition-like" effects over the stimulated area, while higher frequencies of five or more Hz are associated with "excitatory-like" phenomena [6]. Newer TMS paradigms have been developed that are able to modify cortical excitability in significantly less time (20–190 seconds) [7]. Of those, one of the most popular is the theta burst stimulation, where high frequency pulses (3 pulses at 50 Hz) are applied repeatedly at intervals of 200 ms, delivered as a continuous (cTBS) or intermittent (iTBS) train. The former protocol is characterized as being "inhibitory" and the latter being "excitatory," according to the changes produced in MEPs size (**Figure 1**). This is admittedly an oversimplification, as there is a wide heterogeneity of response between subjects. The final biological effect of TMS is determined by the vector summation of all changes in the excitability of cortical interneurons, the status of the neurons prior to stimulation, the intrinsic properties and geometrical orientation of fibers within the cortical region, pharmacotherapy interactions, etc.

2.2. TMS proposed mechanisms of action for therapy

While a single session of TMS induces rather short-term effects (minutes up to hours) [9], the application of rTMS over time (several days/weeks) generates significantly longer lasting biological outcomes (in the order of weeks or a few months) [10]. The evidence of clinical changes that persist well beyond the time of stimulation is the foundations of therapeutic and rehabilitative perspectives. Two types of TMS-induced effects are essentially recognized: short-term and medium-term. Although the molecular mechanisms underlying these changes are not yet conclusive, several theories have been postulated. Short-term effects appear to be related to immediate changes in neuronal ionic conductivity induced by electrolysis phenomena resulting from propagating electromagnetic currents [11]. An additional proposed mechanism behind short-term effects is the release of neurotransmitters. It has been demonstrated that high-frequency rTMS applied over the left dorsolateral prefrontal cortex is associated with a tonic release of dopamine in the ipsilateral caudate and orbitofrontal cortex [12]. Meanwhile, medium-term effects of TMS are believed to be mediated by neuroplastic phenomena. The term "neuroplasticity" defines the ability of the CNS to respond to a broad spectrum of extrinsic and intrinsic stimuli through a functional, dynamic reorganization of its structures and connections. The epicenter of neuroplastic phenomena is the synapse. Increased synaptic strength, synaptogenesis and enhanced selectivity in the recruitment of neural pathways are

http://dx.doi.org/10.5772/intechopen.75052

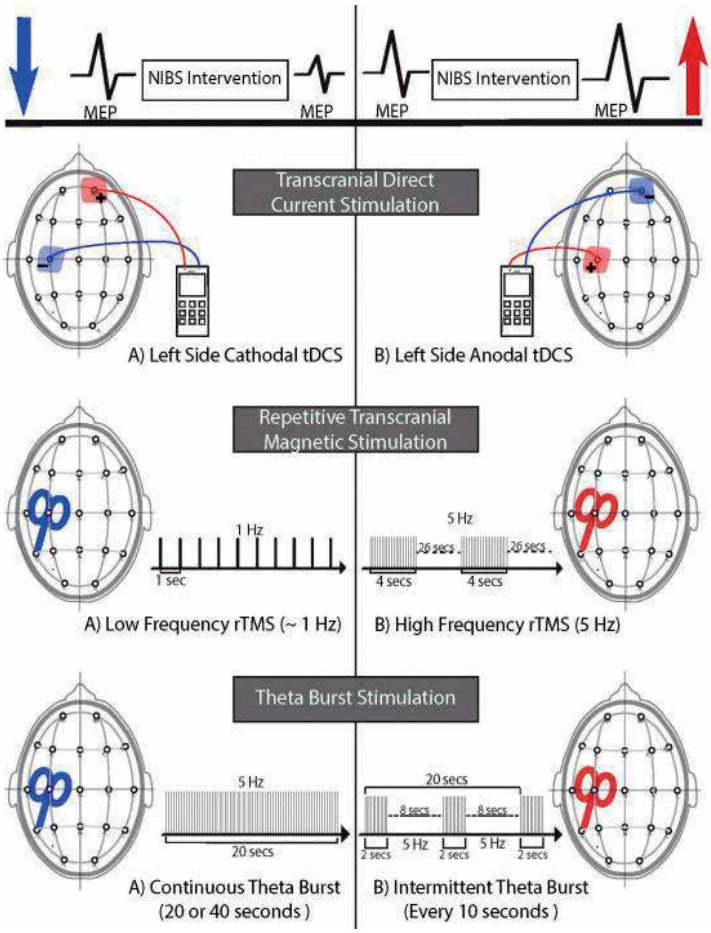

Figure 1. Illustration of motor evoked potential (MEP) changes induced by different types of NIBS over motor cortex. Blue colored arrow (left side) represents inhibitory and red colored arrow (right side) excitatory effects on MEPs.

some of the main mechanisms involved in neuroplasticity (**Figure 2**). It is believed that TMS can harness plastic phenomena by modulating long-term potentiation (LTP) and long-term depression (LTD) like phenomena. The molecular bases of such phenomena are likely to be found in the activation of the postsynaptic N-methyl-D-aspartate (NMDA) receptor [2, 8]. The calcium-mediated signal moderated by this receptor involves the activation of a complex subcellular pathway leading to downstream changes in protein synthesis and, consequently, to functional and structural changes in synaptic efficiency.

Finally, changes in gene expression of neurotrophic molecules as well as increased neurotrophic signaling are considered to be involved in the induction of more sustained effects of TMS. The knowledge concerning these effects at the molecular and cellular level is still very limited. Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophic family that has been demonstrated to exert neurotrophic and neuroprotective effects both *in vitro* and *in vivo*. In animal models, a significant increase in BDNF mRNA levels has been found in the hippocampal areas, parietal and piriform cortex following high frequency rTMS paradigms [13]. It has also

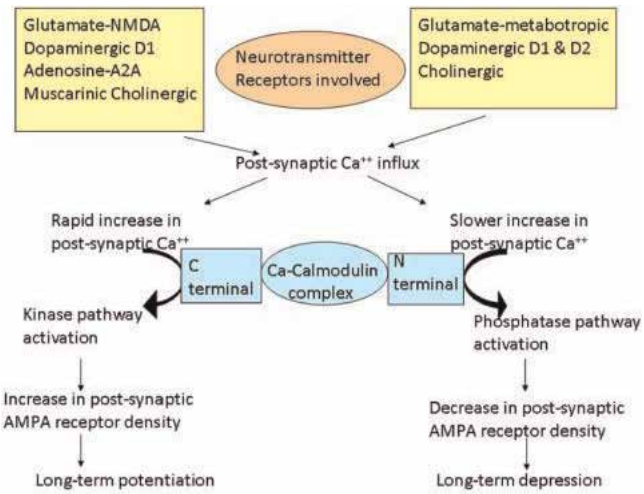

Figure 2. Schematic representation of the cascades of events involved in long-term potentiation (LTP) and depression (LTD). Reproduced with permission from Udupa and Chen [8].

been posed that rTMS could increase BDNF tropomyosin receptor kinase B (TrkB) signaling in rats and humans by increasing the affinity of BDNF for its receptor TrkB [14]. These evidences support a potential role of rTMS in providing long-term neuroprotective effects, although the exact neurochemical mechanisms underlying these properties remain to be fully elucidated.

2.3. Transcranial electric stimulation

Transcranial electric stimulation (tES) includes different NIBS techniques increasingly used for modulation of CNS excitability in humans. The principal mechanism of action of tES is a sub-threshold modulation of neuronal membrane potentials, which alters cortical excitability depending on the current flow direction through the target neurons [15]. For these reasons, tES techniques are more properly regarded as "neuromodulation" techniques, as, instead of inducing an activity in resting neuronal networks, they modulate spontaneous neuronal activity depending on the previous physiological state of target cells. Among different tES techniques, transcranial direct current stimulation (tDCS) is the best characterized and most widely used in both clinical and research settings. tDCS involves the application of a low amplitude direct current (DC) via surface electrodes on the head for a predetermined time in a painless, safe manner (**Figure 3**) [3]. tDCS offers many advantages over other NIBS devices due to a favorable non-invasive, safe profile, portability, tolerability, and cost effectiveness. Several studies have shown that tDCS modulates cortical excitability in the human motor [16, 17] and visual cortex [18]. Studies in young-adult, healthy controls showed that 13 minutes of motor cortex tDCS modifies the amplitude of motor evoked potential (MEP) for the subsequent 90 minutes [16]. Furthermore, pharmacological blocking of N-methyl-D-aspartate (NMDA) receptors prevents long lasting effects of tDCS on cortical excitability, suggesting tDCS may recruit NMDA receptor-dependent plasticity. However, in animal models of tDCS, stimulation intensities comparable to those modeled in humans are not directly associated to LTP phenomena [19]. It is believed that tDCS alone produce

Figure 3. Example of transcranial direct current stimulator (tDCS) setup; mini-clinical trials (mini-CT) Unit, Soterix Medical©.

only a subliminal neural hyperpolarization (under the cathode) or depolarization (under the anode), reducing/increasing in turns the responsiveness of the target neurons to the on-going afferent brain activity. Importantly, when combined with a second input, tDCS could results in powerful induction of LTP or LTD like phenomena. The mechanisms underlying this potential synergistic effect are not fully known, but they may rely on associative plasticity. It is known that task-specific training can induce task-specific neuronal changes based on use-dependent plasticity phenomena [20]. Therefore, the combination of behavioral tasks and tDCS may offer significant chances to achieve neuroplastic changes. The task-dependency of tDCS may influence the inter-individual variability of behavioral or neurophysiologic outcome observed after stimulation [21].

Many strategies are currently under investigation with the aim of boosting neurorehabilitation: NIBS, motor learning theories, behavioral interventions, robot-assisted rehabilitation, pharmacological agents, and neural engineering. It is likely that the optimal combination of these different approaches shall modify the science of neurorehabilitation in the future.

3. Safety of non-invasive brain stimulation

Since there are several methodological and technological differences between the different NIBS types, the tolerability, adverse effects and safety are addressed separately.

3.1. Transcranial magnetic stimulation general safety

Different side effects resulting from the application of TMS have been reported in the literature. The international safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research [6] have listed them according to their respective frequency. Common side effects include transient headache, local pain, neck pain, toothache, and paresthesia. Pain duration is usually limited, lasting up to few hours after the session, and it can be commonly relieved with acetaminophen or other over-the-counter medications. Less common adverse effects include transient hearing changes, transient cognitive/neuropsychological changes, syncope (as epiphenomenon and not related to a direct brain effect), and transient acute hypomania (after left prefrontal rTMS). Rare adverse effects reported include changes in blood levels of thyroid stimulating hormone and lactate, and seizures. Seizure activity has been reported mostly with high-frequency (HF) rTMS. TMS-induced seizures are self-limited and are not reported to have permanent sequelae. High frequency TMS has 1.4% crude risk estimate of inducing seizures in epileptic patients and less than 1% in non-epileptic subjects [22]. There is a theoretical risk of inducing currents in electrical circuits when TMS is delivered in close proximity of electric devices (e.g., pacemakers, brain stimulators, pumps, intra-cardiac lines, cochlear implants) which can cause malfunction of these devices.

3.2. Transcranial magnetic stimulation safety in Parkinson's disease population

From 211 studies published in PubMed regarding the use of TMS in Parkinson's disease patients from 1993 to October 2017, the most common adverse events (AEs) were scalp pain and headache. Most of these happened during high frequency rTMS sessions. Other less commonly reported AEs in PD include neck pain, tinnitus, and facial twitching. One study reported subclinical worsening of complex and preparatory movement as measured by spiral drawing impairment in patients after rTMS and worsening of resting tremor in one patient [41]. Rare AEs possibly related to TMS reported were transient fatigue, mild transient visual hallucinations, and transient hypotension [28]. One study reported a subject who experienced worsening in pre-existing lower back pain (**Table 1**) [37]. In our neurostimulation lab, we had one report of mild transient low mood [23] and one serious AE represented by an ischemic stroke. The ischemic stroke event was due to carotid disease (atherosclerosis) and was deemed unrelated to the study, though [26]. As an important note, to date, there are no reports of seizures induced by TMS among Parkinson's disease patients.

3.3. Safety concerns regarding "Novel" stimulation protocols

3.3.1. Deep repetitive transcranial magnetic stimulation

This technique utilizes deep TMS coils (called H-coils), which, due to a much slower decay of the electric field as a function of distance, allows for the stimulation of deeper brain regions. One study of deep rTMS [29] found that mild transient dyskinesias following stimulation to be a relatively frequent side-effect (15% of PD patients in that study). Dyskinesias happened

Study	TMS parameters	N	Adverse events (AEs)
ExerTMS (2017) [23]	HF rTMS	8	Scalp pain (n = 2), neck pain (n = 2), low mood (n = 1)
LocoTMS (2017) [24]	HF rTMS	5	Neck pain (n = 1)
Chang et al. (2017) [25]	HF rTMS ± tDCS	32	Headache (n = 1)
Brys et al. (2016) [26]	HF rTMS	61	Headache and neck pain (n = 34), ischemic stroke (n = 1)
Shin et al. (2016) [27]	HF rTMS	18	Facial twitch (n = 1), headache (n = 1)
Cohen et al. (2016) [28]	HF rDTMS	19	Scalp discomfort (n = 9), transient fatigue (n = 3), transient visual hallucinations (n = 1)
Spagnolo et al. (2014) [29]	HF rDTMS	27	Transient hypotension (n = 1), headache (n = 1), mild dyskinesia affecting only with LID (n = 4)
Shirota et al. (2013) [30]	LF rTMS	106	Tinnitus (n = 1), headache (n = 1)
Murdoch et al. (2012) [31]	HF rTMS	20	Headache (n = 2)
Benninger et al. (2011) [32]	iTBS	13	Transient tinnitus (n = 1), local scalp pain (n =?)
Pal et al. (2010) [33]	HF rTMS	12	Headache (n = 2)
Benninger et al. (2009) [34]	spTMS	10	Ipsilateral CN VII stimulation
Rothkegel et al. (2009) [35]	LF/HF rTMS	22	Headache (n = 2), nausea(n = 1)
Cardoso et al. (2008) [36]	HF rTMS	11	Headache (n =?)
Hamada et al. (2008) [37]	HF rTMS	55	Increased lower back pain (n = 1)
Khedr et al. (2006) [38]	HF rTMS	55	Headache (n =?)
Lomarev et al. (2006) [39]	HF rTMS	18	Intolerable scalp pain (n = 1)
Dragasevic et al. (2002) [40]	LF rTMS	10	Burning sensation in the scalp(n = 4), headache(n = 3)
Boylan et al. (2001) [41]	spTMS HF rTMS	10	Worsening of tremor (n = 1), scalp discomfort(n = 3), subclinical worsening of complex and preparatory movement (n = 5)

HF: high frequency; iTBS: intermittent theta burst stimulation; LF: low frequency; LID: levodopa induced dyskinesia; rDTMS: repetitive deep TMS; spTMS: single pulse TMS; rTMS: repetitive TMS; tDCS: transcranial direct current stimulation.

Table 1. Reported adverse events in studies involving TMS use in Parkinson's disease patients.

while the patients were OFF-medication and only in patients suffering from levodopa-induced dyskinesias (LID) prior to the stimulation. The same study also reported headache and one case of transient hypotension [29]. In another study, common effects reported included scalp discomfort and transient fatigue, with one episode of mild visual hallucinations [28].

3.3.2. Theta burst stimulation

To date, 19 studies have applied different patterned theta burst TMS to patients with PD. Among these studies, there is only one report of transient tinnitus (<5 minutes) and local pain during stimulation [32]. Overall, these findings seem to indicate that TBS does not carry additional risks with respect to conventional TMS protocols in PD.

3.3.3. Repetitive TMS preconditioned by tDCS

Both high frequency and low frequency rTMS preconditioned by tDCS have been used in PD. From these studies [25, 42, 43], only one occurrence of mild headache has been reported [25].

3.3.4. TMS in PD patients with implanted deep brain stimulators

Eighteen studies have been conducted in DBS-implanted PD patients with no reported AEs. Of note, electroconvulsive therapy, which uses much higher current than TMS, has also been performed in DBS patients without adverse effects. There is currently no evidence supporting the risk of heating or displacing DBS leads, but TMS has demonstrated induction of secondary currents in a DBS wire if closely applied to it [44, 45]. The main factors in determining the risk of inducing eddy currents in the DBS device seem to be the distance between the TMS coil and the DBS lead, as well as the number of loops of the wire over the DBS lead [46, 47]. Additional safety studies should be conducted to evaluate the magnitude of induced voltages and induced currents generated by TMS in implanted stimulator systems like DBS and cortical stimulation with epidural electrodes. According to current international safety guidelines [6], TMS should only be done in patients with implanted stimulators if there are scientifically or medically compelling reasons justifying it.

3.3.5. High frequency rTMS beyond 25 Hz

Rossi and colleagues seminal paper in 2009 had shown safety consideration with HF rTMS only up to 25 Hz [6]. Benninger et al. performed 50 Hz sub-threshold rTMS over the motor cortex for up to 2 seconds in 10 PD patients with only one withdrawal due to uncomfortable facial muscle stimulation [34]. A second study was then carried out with 6-second train duration where 13 PD participants received 50 Hz rTMS. No AEs and no EMG/EEG pathological increases of cortical excitability or epileptic activity were reported [48].

3.4. Transcranial direct current stimulation general safety

The protocol of stimulation (therapeutic or experimental) constitutes a critical determinant of safety, as well as the inclusion/exclusion criteria and protocol technical execution. Bikson et al. reported that from aggregated data of 33,000 sessions over 1000 subjects receiving repeated tDCS sessions, no evidence for irreversible brain injury was produced by conventional tDCS protocols within a wide range of stimulation parameters (≤40 minutes, ≤4 mA, ≤7.2 Coulombs). This includes a wide variety of subjects, including persons from potentially vulnerable populations [49]. In contrast to TMS, tDCS does not trigger neuronal depolarization; this might account for the unlikelihood of tDCS causing seizures. Although one seizure was reported in an epileptic, 4-year-old boy with cerebral palsy while receiving tDCS [50], this has been, to date, the only possibly tDCS-associated seizure reported. Other plausible causes of his seizure, such as reduced antiepileptic medication at the time and possible interactions with serotonergic medication, were considered.

Commonly reported AEs appear to be of mild intensity and transient duration. In their meta-analysis, Brunoni and colleagues characterized the incidence of AEs in 209 studies published

from 1998 until August 2010 [51]. Of these 209 studies, 117 were compared for active tDCS vs. 82 sham tDCS studies and showed side effects of tingling (22 vs. 18%), headache (15 vs. 16.2%), burning sensation (9 vs. 10%), itching (39 vs. 33%), and discomfort (10 vs. 13%) [51]. Results suggested that some AEs, such as itching and tingling, were more frequent in the tDCS active group, although this was not statistically significant. The authors disclosed a selective reporting bias for reporting, assessing, and publishing AEs of tDCS that hinders further conclusions. The authors raised awareness of the need to improve systematic reporting of tDCS-related AEs.

The local effects of tDCS on the skin are not believed to be necessarily linked to the hazards involving the underlying brain tissue. Several causative factors for skin lesions have been proposed, including electrode position (the front side of scalp due to curvature and lack of hair), skin conditions, allergic predisposition, skin preparations, high skin impedances, high electrical currents, duration of stimulation, repeated sessions, small electrodes (high current density), electrode shape, dry electrodes, inadequate fixation of electrodes, non-uniform contact pressure of electrodes to skin, extensive skin heating, solution salinity of electrode sponges, sponge shape, and deterioration of the sponges [52]. Other notable, non-skin AEs that have been reported are nausea, dizziness, and sleepiness [53, 54]. Several studies conducting tDCS over DLPFC reported hypomania or mania in unipolar and bipolar depression treatment trials, but these AEs cannot be fully attributed to tDCS [55–57]. The risk of hypomania or mania in depressed subjects receiving tDCS might not be generalizable to a different population or different brain location; however, it could be a risk if a study does not exclude depressed participants.

3.5. Remotely supervised transcranial direct current stimulation

Recent trials have developed tDCS as a 'telemedicine protocol.' This paradigm utilizes computer videoconferencing for real-time monitoring between the study subject and a study technician [58]. This innovative approach is intended to increase compliance and facilitate research participation by allowing patients to receive therapy in the comfort of their homes. While traveling to clinic or research labs for a tDCS session can present an obstacle to subjects and their caregivers, with modified devices and headgear, tDCS can be administered remotely under clinical supervision, potentially enhancing recruitment due to convenience, while still maintaining clinical trial and safety standards [59]. Perhaps the most promising and tested paradigm is remotely supervised tDCS (RS-tDCS). RS-tDCS has been proven to be safe, feasible, and acceptable for patients with multiple sclerosis [60–62].

3.6. Transcranial direct current stimulation safety in Parkinson's disease population

Current published studies utilizing tDCS in PD patients have shown mostly mild and expected adverse events [63], with only one reported event of skin burn (similar to first degree burn) [63]. The skin burn was deemed due to mal-positioned electrodes and resolved without sequela in 3 days. There is no specific provision or precautions for tDCS in PD. However, as previously pointed out by Brunoni et al., as almost half of studies do not report presence/absence of AEs, it is indispensable that clinical research document and report AEs in an active,

systematic fashion in order to guarantee that tDCS is indeed a safe technique [51]. Our neurostimulation lab is currently conducting clinical trials with RS-tDCS for PD. Our experience has been very positive with regard to feasibility, safety, and acceptability of RS-tDCS in PD [64, 65]. Further trials of RS-tDCS need to be conducted to corroborate the feasibility and safety of remote videoconferencing tDCS sessions. At-home, tele-monitored tDCS therapy (e.g., RS-tDCS) could become crucial to ease the development of multicenter initiatives with longer period of stimulation and minimizing participant's burden.

In summary, the safety and tolerability of tDCS can be maximized by following standard procedures, defining optimal stimulation parameters, and following good clinical and good research practice implying adequately trained personnel, constant checking of stimulation settings, careful selection of subjects, prompt and systematic reporting of AEs, and regular supervision of tDCS equipment. The international safety guidelines for tDCS neuromodulation [19] emphasizes the importance of adequately trained personnel in delivering the stimulation and overseeing all related procedures (i.e., for RS-tDCS). Overall, tDCS is a generally safe technique when used within standardized protocols in a research or clinical setting. However, generalization of safety beyond these settings into different clinical contexts or do-it-yourself (DIY) should be avoided [66]. RS-tDCS standardized framework for safety, tolerability, and reproducibility, once established, will allow for translation of tDCS clinical trials to a greater size and range of patient populations.

4. Potential applications and therapeutic effects of NIBS in PD

There has been cumulative evidence supporting beneficial effects of TMS and tDCS in PD. However, several limitations have obscured the evidence-based generalizability of these results. Main limitations are wide methodological heterogeneity in study designs (outcomes, eligibility criteria, intervention parameters, brain targets, etc.) and exploratory designs with small sample sizes in the majority of the studies. As TMS research is significantly more advanced in terms of number of studies and Class I multicenter initiatives, TMS and tDCS therapeutic evidence will be revised separately.

4.1. Effects of TMS in PD

Several systematic reviews and meta-analyses support the positive therapeutic effect of TMS in PD [67, 68]. The wide use of the Unified Parkinson's Disease Rating Scale (UPDRS) across most studies enabled results to be compared through meta-analysis [67, 69]. UPDRS is likely the most widely used assessment for PD and combines elements of four scales to produce a comprehensive and flexible tool to monitor the course of Parkinson's and the degree of disability. The cumulative score will range from 0 (no disability) to 199 (total disability). Motor UPDRS (part III) is usually administered by a healthcare professional and scores the motor performance in a series of items, including rigidity, bradykinesia, and tremor. UPDRS part II, on the other hand, is a self-evaluation of activities of daily living "during the last week." It is important to point out that the beneficial TMS effects are mostly seen in motor scores in the

UPDRS part III; as such, this might question the overall functional relevance and impact in quality-of-life. The average improvement of motor UPDRS sub-score in these clinical trials ranged from −2.7 to −6.4 points and mainly reflected improvements in bradykinesia and rigidity. The minimal clinically important change of motor UPDRS sub-score has been proposed to be between 5 and 6 points [70, 71].

Chou and colleagues conducted subgroup analysis of clinical trials and showed that the effect sizes estimated from high-frequency rTMS targeting the primary motor cortex (SMD, 0.77; 95% CI, 0.46–1.08; P < .001) and low-frequency rTMS applied over other frontal regions (SMD, 0.50; 95% CI, 0.13–0.87; P = .008) were significant. The effect sizes obtained from the other 2 combinations of rTMS frequency and rTMS site (i.e., high-frequency rTMS at other frontal regions: SMD, 0.23; 95% CI, −0.02 to 0.48, and low primary motor cortex: SMD, 0.28; 95% CI, −0.23 to 0.78) were not significant. Meta-regression revealed that a greater number of pulses per session or across sessions are associated with larger rTMS effects [69].

The two more recent multicenter randomized clinical trials of TMS for PD were not included in the referenced reviews. Shirota et al. [30] explored the efficacy and stimulation frequency effect of rTMS over the supplementary motor area (SMA) in PD. Results showed a decrease (improvement) of 6.84 points in the UPDRS part III in the 1 Hz group at the last follow up (12 weeks post-intervention). Sham stimulation and 10 Hz rTMS improved motor symptoms transiently, but their effects disappeared in the observation period. The magnitude of improvement is similar to prior HF rTMS studies; however, it was only significant at the last follow up. Interestingly, the preliminary results of a prior trial from the same group showed that HF rTMS was significantly better than LF over SMA [37]. A final interesting observation is that rTMS was applied once weekly for 8 weeks rather than daily session. These findings have not been replicated yet.

The latest large multicenter clinical trial was published in 2016 by Brys et al. [26]; the study innovated "multifocal stimulation" in PD patients suffering from comorbid depression. It compared motor cortex stimulation with dorsolateral pre-frontal cortex (DLPFC) stimulation, both alone and in combination. The results provided Class I evidence of motor beneficial effects of HF rTMS over motor cortex, but failed to prove synergistic effects when combined with DLPFC. The magnitude of the improvement (−4.9 points in the UPDRS-III), was close to a minimal clinically important change on the UPDRS-III [71] but slightly below that found in meta-analyses (−6.4 and −6.3 points) [69, 72]. It is worth mentioning that the effects were only significant at 1-month follow up and not significant in the following observations at three and 6 months distance respectively. These extended follow-up period results raise concern on the sustainability of significant improvements beyond 1 month. Despite the amount of data regarding the efficacy and safety of this technique in relieving motor symptoms of PD, rTMS has not yet been systematically assessed as a potential treatment for FoG. An initial report by Rektorova and colleagues found no significant effect on OFF-related FoG in six PD patients treated with five sessions of high-frequency rTMS over the DLPFC and primary leg motor area [73]. However, a later double-blind cross-over study on 20 patients with FoG investigating the effects of a single session high frequency rTMS did suggest efficacy [74]. As recently observed, the contribution of NIBS alone or combined with neurorehabilitation to address this highly

disabling phenomenon remains to be systematically assessed through well-powered, well-designed and reproducible studies [75].

The use of rTMS for the treatment of dyskinesias is limited to small studies showing contradictory findings, with either LF rTMS over M1 [76, 77] or LF rTMS over SMA [78, 79].

In 2014, a group of European experts in TMS were commissioned to revise all available trials to elaborate evidence-based guidelines for the therapeutic use of rTMS [80]. This included randomized controlled trials with at least 10 subjects receiving active stimulation, along with at least 2 comparable studies (same cortical target and same stimulation frequency), published by independent groups before the end of March 2014. Results concluded possible antiparkinsonian effect of HF rTMS over motor cortex delivered bilaterally. Other results were: no recommendation for dyskinesias and a probable antidepressant effect on HF rTMS over the left DLPFC in PD.

Novel paradigms of pairing TMS with other rehabilitation methods to try synergies and optimizing rehabilitation have recently been explored. Experimental protocols carried out in our neurostimulation lab have combined TMS with motor skill learning [81], physical therapy [35], aerobic exercise [23], and finally, with treadmill training [82]. Larger studies will need to be conducted to further validate these paradigms. Optimal treatment parameters remain elusive. Standardization of PD outcomes, of TMS methodologies and bigger multicenter collaborative initiatives with long follow-up periods are [12] needed to demonstrate the real therapeutic potential of TMS in PD.

4.2. Therapeutic applications of tDCS in PD

tDCS has been tested to promote motor learning in healthy adults and stroke patients [83, 84]; this technique has also been explored as a treatment of migraines, aphasia, multiple sclerosis, epilepsia, tinnitus, schizophrenia, and dystonia with unclear or insufficient beneficial evidence for recommendation [85]. According to recent evidence-based guidelines for the therapeutic use of tDCS (including studies published before the end of the bibliographic search on September 1, 2016), only some types of chronic pain, fibromyalgia, depression, and craving have shown to benefit from the neuromodulation, with possible or probable recommendation levels. tDCS for PD has no formal recommendation; however, "no recommendation" means the absence of sufficient evidence to date, but not the evidence for an absence of effect [83]. Also to be noted, studies that have not been replicated were not included for analysis in this evidence-based review. tDCS seems to induce some beneficial effects in motor symptoms in PD, but studies are needed to replicate these results [86].

A Cochrane review by Elsner et al. [87], found no evidence of effect as measured by UPDRS global change in two studies and low quality evidence on motor impairment as measured by means of UPDRS Part III when real stimulation was compared vs. sham [63, 88]. Two studies specifically investigated the impact of tDCS on quantitative gait parameters [63, 89] and showed no significant changes in walking speed. There have been no reported studies exploring the efficacy of tDCS on tremor. The reduction of OFF-time and ON-time hampered by dyskinesias was analyzed in one study conducted on 25 subjects, resulting in no significant benefit [63]. In addition, health-related quality-of-life variables on both physical and mental

domains were investigated, again with no significant effect [63]. As concluded by Elsner et al., "the methodological quality of these studies needs to be improved with particular respect to the risk of allocation concealment, blinding of personnel and intention to treat analysis" [87].

The importance of non-motor features in PD has been increasingly recognized. A particularly active area is the application of tDCS to enhance cognitive function. Cognitive impairment represents a highly disabling non-motor symptom in patients with PD, and several studies in patients with Alzheimer's disease suggest that tDCS could improve memory performance [90, 91]. A few trials have been expressly designed to investigate the therapeutic potential of tDCS on cognitive function in patients with PD with mostly (but not exclusively) using neuromodulation of DLPFC [92–94]. Furthermore, fatigue is a frequently under-recognized non-motor symptom in patients with PD. So far, tDCS over DLPFC has been demonstrated to improve fatigue in other neurological conditions, including MS [95–97]. It seems therefore plausible that analogous stimulation settings could provide similar benefits in patients with PD, although this hypothesis remains to be confirmed through appropriately designed clinical trials (ClinicalTrials.gov identifier: NCT03189472).

5. Non-invasive brain stimulation challenges

The major limiting factors to the extensive clinical application of NIBS technologies are inherent to methodological properties of trials. The body of currently available data mainly rests on small-sized studies carried out with exploratory designs. As such, these studies are known to be prone to the risk of type I and type II statistical errors. Usually, a type I error leads to establish a supposed effect or relationship when, in fact, the null hypothesis is true. Conversely, a type II error leads to erroneous acceptance of the null hypothesis when this is, in fact, false. The best way to control for these errors is to design appropriately sized studies through power calculations based on the estimated magnitude of effects. Alternatively, adaptive designs can be conducted to allow for a flexible increase of the sample along with the trial implementation. This strategy, however, can further complicate the final interpretation of data. A second order of methodological limitation is represented by unavoidable differences in stimulation parameters between trials (i.e., stimulation location, frequencies, coil geometry, number of pulses, number of sessions, specific population, follow-up time, electrode montage, sponge sizes, etc.). These differences result in a commonly limited comparability between studies. At minimum, it is imperative for all NIBS trials to exhaustively disclose the followed stimulation protocol in all its components, thus maximizing comparability and reproducibility. Further, stimulation parameters should be chosen and refined on the basis of biologically plausible hypotheses, and experimental assumptions should be modeled on the pathophysiology of the targeted phenomena. Random target stimulation and "trawl fishing" experimental designs are likely to be inconclusive or to result in poor cost/effectiveness. Negative studies should be adequately reported and acknowledged to improve publication bias and expand knowledge among the scientific community. A clear description of placebo- or sham-controlled method should always be provided and all potential limitations of blinding procedure disclosed. For example, the use of non-realistic sham coils in a cross-over design can

compromise the blinding of the study. Measures to assess adequate masking/blinding procedures should be incorporated into the trial, for example through the administration of specific questionnaires. Most of the original trials published in the literature lack double-blind controlled designs. This limitation has been conveniently weaning off over the past decade as a growing number of properly controlled NIBS trials flourished. Interestingly, newly designed coils can now allow for triple blinded designs where the subject, the investigator, and the technician are unaware whether real or sham stimulation is delivered. The use of appropriate and comprehensive clinical outcome to assess efficacy constitutes another significant challenge. A broad spectrum of symptoms could be potentially affected by NIBS. In order to capture clinically meaningful effects, quality-of-life scales and other tools exploring subjective improvements on ADLs should be incorporated to assess NIBS potential beyond the simple motor effect as quantified by UPDRS-III. Standardization of outcomes can also facilitate further meta-analysis. Finally, knowledge about NIBS and its therapeutic potential on movement disorders could be boosted by collaborations across involved laboratories and multicenter initiatives. In parallel, adequate training of personnel to refine operator's expertise and skills should be provided in a standardized fashion across academic centers [19].

6. Conclusions

To summarize, clinical effects of NIBS can be attributed to complex and likely interconnected phenomena, including the normalization of cortical excitability, the modulation of connectivity between neuronal networks and the induction of neuroplastic phenomena. The substantially safe, reproducible, and non-invasive nature of NIBS makes these techniques of appealing interest for the study and treatment of various neurological and psychiatric disorders, including PD. For TMS, the pooled evidence suggests that rTMS improves motor symptoms of PD. Overall, HF rTMS over M1 and LF rTMS over SMA appears effective. The motor improvement in large multicenter clinical trials is around the minimal clinically important change of motor UPDRS. There are controversial findings in a few small studies for dyskinesias. There is insufficient data regarding the effects of rTMS for improving health-related quality-of-life, disability and activities of daily living. These data would help to better determine the clinical relevance for motor improvements. The currently available evidence supporting the use of tDCS neuromodulation in patients with PD is limited to small, single-center studies exploring different symptoms of the disease mainly through heterogeneous experimental methodologies. There is need for appropriately designed, directly comparable and well-powered trials to better characterize the therapeutic potential of this technique in this specific population. Despite these limitations, tDCS still holds much promise for a potential therapy as it is a relatively inexpensive, portable, and easy to perform technology.

Acknowledgements

The authors wish to acknowledge Miss Rebecca M. Friedes, for her contribution in editing the manuscript. Authors did not receive any funding or monies for the preparation of the manuscript.

Conflict of interest

The authors declare that they have no competing interests and report no disclosures relevant to the manuscript.

Notes/Thanks/Other declarations

The authors would like to thank the Marlene and Paolo Fresco Institute for Parkinson's and Movement Disorders and the Neurology department at NYU Langone Health for the support provided to the TMS and Neurostimulation laboratory.

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Chapter 5

Development of Neural Stem Cell-Based Therapies for Parkinson's Disease

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.73870

Abstract

Neural stem cell (NSC)-based therapies, such as cell transplantation, are an emerging strategy for restoring neuronal function in Parkinson's disease (PD), which is characterized by a profound and selective loss of nigrostriatal dopaminergic (DA) neurons. Advanced researches on the microenvironment of grafted cells will promote clinical applications of NSCs for neurological disorders. A novel cell culture model of the neurovascular network was therefore devised to investigate autocrine, paracrine, and juxtacrine signaling in the neurovascular unit generated by NSCs and vascular endothelial cells. Preclinical studies using cutting-edge technologies, including cellular reprogramming, advancement in scaffolds for brain tissue engineering, image-guided injection, and noninvasive monitoring of tissue regeneration will pave the way for successful clinical trials of NSC-based therapies for PD. Once the implanted or regenerated DA neurons are integrated into the existing nigrostriatal DA pathway, the symptoms of PD can potentially be alleviated by reversing characteristic neurodegeneration.

Keywords: neural stem cell, Parkinson's disease, endothelial cell, neurovascular unit, regenerative medicine, tissue engineering, cell transplantation

1. Introduction

Parkinson's disease (PD) is the most common neurodegenerative movement disorder, and its prevalence reaches 0.3% of the entire population in industrialized countries [1]. PD prevalence is increasing with age, affecting 1% of the population above 60 years and 4% in those aged over 80 [2]. Since the clinical trial of neural stem cell (NSC) transplantation therapy has shown promising results for stroke patients [3], the NSC-based therapy could be a potential treatment

for restoring neuronal function for PD patients. A better understanding of pathophysiology of PD, establishment of valid and effective NSC lines, and successful clinical trials will point to a novel neuroregeneration strategy to complement current medical treatment and deep brain stimulation.

Advances in the pathophysiology of PD have expanded our traditional knowledge that it is characterized by a profound and selective loss of nigrostriatal dopaminergic (DA) neurons. PD could be considered a developmental disorder with evidence beyond neurodegeneration, regarding relationships among deregulated neurogenesis, disease onset, and its progression. The numbers of proliferating NSCs, for instance, have been found decreased in the PD-affected postmortem brain [4, 5], but evidence of a link between altered proliferation of NSCs, functional DA neurons, and neurological deficits remains insufficient. Besides typical motor symptoms, including asymmetrical bradykinesia, rigidity, postural instability, and resting tremors, patients may have nonmotor symptoms, such as dementia, sleep disturbance, and autonomic dysfunction. Hence, public health education and routine physical examinations are substantial for early diagnosis and intervention.

NSCs preserve the ability to self-renew and differentiate into all neural lineage cells, and they are regarded as a potential graft for cellular transplantation. Reducing the possibility of tumorigenesis has to be considered during immortalization of NSC lines which provide a consistency of cell grafting. Furthermore, preclinical studies, such as transcranial injection of NSCs into animal brains with adequate follow-ups, will prove the validity of its clinical application.

Independent ethical and regulatory approval, full financial support from the foundation, and long-term follow-up of systematically collected rigorous measures are the requirements for conducting clinical trials for NSC-based therapies in PD. Appropriately transparent processing with governmental approval could encourage patient cooperation according to experience from cell transplantation therapy in other diseases. In this chapter, we will provide a comprehensive literature review as well as the perspectives on NSC applications in PD.

2. Neuronal loss in Parkinson’s disease

The pathological diagnosis of PD has been possibly made since Frederic Lewy described microscopic particles in affected brains as early as 1912, later named “Lewy bodies” [6]. The characteristic pathophysiology of PD includes death of DA neurons in the substantia nigra pars compacta (SNpc), degeneration of DA neurotransmission, and the presence of alpha-synuclein and protein inclusions in neuronal cells that are known as Lewy bodies [7]. In general, more than 50% of DA neurons have been lost before typical symptoms of PD develop [8]. It has been found that a 20% decrease in nigral neuronal cell density in incidental Lewy body disease compared with controls [9]. Additionally, nigral neuronal loss could be observed before the appearance of alpha-synuclein aggregates [9]. A negative correlation between neuronal density and local alpha-synuclein burden in the substantia nigra was therefore evident in PD patients. Most importantly, stage-dependent nigral neuronal loss and local burden of alpha-synuclein pathological conditions are closely coupled during disease progression of PD.

The diagnosis of PD can be made through the detection of mutations in specific genes responsible for familial PD in the era of molecular biology. But only about 10% of diagnosed patients are found carrying identifiable pathological mutations, and the majority of PD cases are sporadic [2]. Several of the PD-associated genes are related to mitochondrial dysfunction although most are of unknown or poorly understood function. Three of the genes associated with a recessive, early-onset form of the disease (*DJ-1*, *PINK1*, *Parkin*) are directly linked to mitochondrial function, providing a potential connection with changes associated with aging [10]. DJ-1 is a mitochondrially enriched, redox-sensitive protein, and it is able to signal oxidative challenges and potentially coordinate a variety of mitochondrial oxidative defense mechanisms [11, 12]. Parkin and PTEN-induced putative kinase 1 or PINK1 also have mitochondrial roles [13, 14].

The strongest risk factor in PD is age, beyond the other three best-documented pan-cellular factors, including genetic mutations, environmental toxins, and inflammation [2, 15]. It is widely speculated that declining mitochondrial function is a key factor why age is such a strong risk factor [10, 16]. However, the pattern of neuronal pathology and cell loss in PD is difficult to explain without cell-specific factors. It has been proposed that the opening of L-type calcium channels during autonomous pacemaking results in sustained calcium entry into the cytoplasm of SNc DA neurons and accordingly the increase in mitochondrial oxidant stress and susceptibility to toxins [15]. This cell-specific stress could increase the negative consequences of pan-cellular factors. Therefore, antagonists for L-type calcium channels have been proposed to complement current attempts to boost mitochondrial function in the early stages of PD [17], but there is still lack of strong evidence in its therapeutic effects.

3. Neural stem cells and adult neurogenesis

In the adult mammalian brain, NSCs are largely restricted to two regions: the subependymal zone (SEZ) of the lateral ventricles and the subgranular zone (SGZ) of the dentate gyrus in the hippocampal formation [18, 19]. The NSC niche can be regarded as a specialized neurovascular unit (NVU) because the vasculature plays an indispensable role for maintaining the stem cell niche [20]. The NSC niche in the adult SEZ contains an extensive planar vascular plexus with specialized properties. Within such a unique NVU, endothelial cells (ECs) exert their influence over NSCs to regulate fate specification, differentiation, quiescence, and proliferation, through direct contact and paracrine signaling [20]. For example, a U-shaped gradient of the soluble factor, stromal cell-derived factor 1 (SDF-1), established by both ependymal and endothelial cells, helps guide SEZ quiescent NSCs moving from the ependymal niche to the endothelial niche, where they are activated [21]. Endothelial factors, including SDF-1, therefore have differential effects on neural progenitor populations. The vessels also produce a laminin-rich extravascular basal lamina, which is organized into branched structures known as fractones, regulating NSC behaviors via direct contact [22]. Interestingly, vascular pericytes in the central nervous system (CNS) have been found to possess the ability of differentiating into vascular and neural lineage cells [23], in addition to the originally defined functions of pericytes, such as controlling cerebral blood flow and limiting blood flow by constricting capillaries [24, 25].

At the interface of neural and vascular compartments in the CNS is the blood brain barrier (BBB), which is the first barrier leading to transport limitations for both cellular and acellular elements. Paul Ehrlich demonstrated the integrity of this barrier first in 1885 when he injected vital dyes into the circulatory system and observed that all organs except the brain and the spinal cord were stained [26]. The integrity of this barrier was attributed to ECs and could be examined with an electron microscope demonstrating the tight junctions [27]. The barrier function of endothelium is considered a hallmark feature when validating models of the BBB. It is also important to assess the barrier function while culturing ECs with other types of cells comprising the NVU in order to investigate adult neurogenesis [28].

The CNS endothelium is not only the inner lining of the blood vessel, but also an active participant in many signaling pathways. Brain-derived neurotrophic factor (BDNF), for instance, is one of the endothelium-secreted factors affecting the behaviors of NSCs [29, 30]. Blood capillaries may regulate NSCs through interactions via collagen IV and laminin in the basal lamina [31]. Blood vessels also provide an access to circulate systemic factors, including glucocorticoids, sex hormones, and prolactins. The barrier properties of the BBB allow only certain molecules to cross the endothelium. The BBB is maintained when endothelium has a prevalence of tight junctions and specific transport proteins. The BBB is characterized by an organ-specific high transendothelial electrical resistance (TEER, up to 5000 ohm·cm^2; in contrast with placental TEER 20–50 ohm·cm^2) [32, 33]. The BBB is the major site for the exchange of molecules between the blood and the CNS, given the small diffusion distance to neurons. Proximity of the finest branches of brain capillaries to individual neurons is typically 8–25 μm [34].

In the neurogenic niche of the mouse brain, the basal processes of NSCs contact the vasculature, and at these sites of contact, a modified BBB exists that lacks astrocytic endfeet and pericytic coverage [20]. Direct physical contact between the brain capillary ECs and the NSCs reflects their intimate relationships. Juxtacrine signaling is therefore essential for devising a NVU model using ECs and NSCs. A NVU with direct contact between NSCs and ECs provides a neurovascular network, where the concentration of soluble factors recently released from nearby cells can remain high locally, and this cannot be observed using the transwell co-culture system. Furthermore, extracellular matrix (ECM) molecules produced by ECs and NSCs, which mediate cell differentiation and tissue morphogenesis, are involved in contact-dependent signaling between NSCs and ECs. The firm adhesion of cells to an ECM is indispensable to a cell culture model of three-dimensional cytoarchitecture for investigating NSCs and adult neurogenesis within a specific NVU.

4. Paracrine and juxtacrine signaling in the neurovascular unit

To devise an advanced NVU model and to promote NSC-based therapies may benefit from studies on the neurovascular development. Accumulating evidence shows that shared molecules and coordinated cellular mechanisms regulate the development of vascular and neuronal systems [35, 36]. Neurogenesis and angiogenesis are also found co-regulated in both embryonic

and adult brains, as well as damaged brains. To date, most of this evidence has been obtained from *in vivo* experiments [37, 38]. Transgenic animal models were commonly used for these studies because relevant human material was still limited. A major technical difficulty in using these primary tissues is that numerous types of cells interact with each other in a very thin compartment. The ECs, for example, are not easily isolated for both qualitative and quantitative biochemical analysis.

Alternatively, *ex vivo* organotypic NVU model systems consisting of the slice of brain and brain ECs have been applied to experiments studying crucial BBB parameters such as TEER and transport mechanisms [39]. Researchers using cortical organotypic slice cultures or SEZ whole mounts [40] are able to observe the cellular interactions within a relatively complete but complicated system. In contrast, experiments using *in vitro* cell culture models of the NVU provide a useful tool in order to disentangle intercellular paracrine, autocrine, and juxtacrine signaling.

4.1. Paracrine signaling

Paracrine signaling is a form of cell-to-cell communication in which the target cell is close to the signaling cell and the secreted and diffusible signal molecule affects only nearby target cells. During CNS development, common signaling molecules guide vascular and axonal outgrowth via paracrine mechanisms, and these factors may have to be considered in NSC-based therapies in PD. For example, growth cones of axons project numerous filopodia that actively extend and retract in response to four families of extracellular guidance cues: ephrins, semaphorins, netrins, and slits [41]. Guidance cues can be divided into attractive or repulsive signals. These cues are cell-membrane-bound acting on nearby axons or secreted forming gradients that influence the trajectories of extending axons [41].

4.1.1. NSC paracrine signaling to EC

The brain vascular system develops from the cephalic mesenchyme through the sprouting of capillaries into the brain parenchyma. This process is regarded primarily as angiogenesis which refers to the *de novo* formation of blood vessels by the sprouting and splitting of vessels already established by vasculogenesis [42]. Vascular endothelial growth factor (VEGF) has been implicated in the control of CNS angiogenesis. The temporal and spatial expression of VEGF is consistent with the hypothesis that VEGF is synthesized and released by the ventricular neuroectoderm and may induce the ingrowth of capillaries from the perineural vascular plexus [43]. Upon entering the CNS parenchyma, blood vessels migrate along a preformed latticework of neuroepithelia and radial glia, which are NSCs and neural progenitors that give rise to differentiated neurons and astrocytes [44].

VEGF is strongly expressed by NSCs in the ventricular zone. VEGF is a key signal orchestrating vascularization of the neuroectoderm [45]. At the tips of vascular sprouts, the leading endothelial tip cells extend filopodia toward hypoxic regions where higher VEGF is produced [46]. Tip cells react to VEGF via VEGF receptor 2 (VEGFR2) expressed on filopodia. Tip cells

produce high levels of the Notch ligand delta-like 4 (Dll4) that activates Notch signaling on adjacent ECs. These ECs then differentiate into stalk cells, which form the stalk of the sprouting vessel with a lumen that allows for blood flow and tissue oxygenation [47]. Stalk cells down-regulate expression of VEGFR2 and VEGFR3 and increase levels of the decoy receptor VEGFR1, thus becoming less sensitive to VEGF [48]. These studies suggest that VEGF/VEGFR2 is one of the signaling pathways involved in angiogenesis and is also important for neurogenesis during CNS development.

4.1.2. EC paracrine signaling to NSC

Vascular-derived neurotrophic factors, such as BDNF, are key factors in the co-ordination of vascular and neural development [49]. In a co-culture experiment using transwell inserts, mouse ECs released soluble factors that stimulated the self-renewal of mouse NSCs and inhibited their differentiation [50]. Depending on the culture condition, mouse ECs may favor maintenance of the progenitor phenotype of mouse NSCs through the production of soluble factors or to promote neuronal differentiation through direct contact [51].

4.2. Autocrine signaling

Autocrine signaling is a form of cell signaling in which a cell secretes a substance that binds to its own surface receptors, leading to changes within the cell. Initially discovered for their role in axon guidance during vessel formation, VEGFs and their high-affinity tyrosine kinase VEGF receptors are now implicated in the development of the CNS [52]. In embryonic mouse forebrain and embryonic cortical neurons grown *in vitro*, VEGF acts as an autocrine survival factor for VEGFR2-expressing postmitotic neurons [53]. In the adult rat brain, VEGFR2 is expressed by neuronal progenitors in the SEZ, and intracerebral administration of VEGF-A stimulates both neurogenesis and angiogenesis in the SEZ and hippocampus [54].

4.3. Juxtacrine signaling

Juxtacrine is a type of cell-to-cell or cell-to-ECM signaling that requires close contact. This stands in contrast to autocrine or paracrine signaling, where a signaling molecule is released and diffused into extracellular space [55]. Cell-to-cell communication between blood vessels and glia cells in the NVU occurs primarily via intervening vascular basement membranes that contain a variety of growth factors and ECM proteins [56].

Juxtacrine signaling is indispensable for neuroblasts migrating along blood vessels as neuroblasts primarily interact with the ECM surrounding astrocyte endfeet in a vasophilic migration model in the mouse brain [57]. In the SEZ neurogenic niche, NSCs differentiate into neural progenitors (NPCs) which have a limited proliferative ability and does not exhibit self-renewal. The relatively quiescent NPCs give rise to rapidly dividing transit-amplifying cells which further differentiate into neuroblasts. These neuroblasts sense microenvironmental cues and migrate tangentially from the SEZ to the olfactory bulb along rostral migratory stream (RMS).

http://dx.doi.org/10.5772/intechopen.73870

5. Restoration of the disrupted neurovascular microenvironment by tissue and cell transplantation

Tissue regeneration or cell replacement for loss of DA neurons is a potential approach for PD. Since the late 1980s, over 300–400 PD patients worldwide have received transplants of human fetal ventral mesencephalic (VM) tissue, which is rich in postmitotic DA neurons [58]. Two double-blind, placebo-controlled trials of VM transplants for PD patients, however, showed variable efficacy and occurrence of side effects, such as "off-medication" and "graft-induced dyskinesias" (GIDs) [59, 60]. It was observed that the PD pathologic process might propagate from host to grafted cells, and the presence of Lewy bodies in grafted neurons suggests host-to-graft disease propagation [61]. Implanted neurons could be affected by the disease process and did not function normally. Parkinson's pathogenesis or GIDs therefore could propagate from host to grafted cells although recipients had experienced long-term symptomatic relief with the majority of grafted cells functioning unimpaired. On the other hand, CNS involvement of graft versus host disease (GvHD) has been found as a cause of CNS disorders after allogeneic hematopoietic stem cell transplantation (allo-HSCT) which is administered systemically [62]. Although transplantation of fetal tissue or stem cells was conducted transcranially instead for PD patients, the rare heterogeneous chronic CNS GvHD symptoms might happen with cerebrovascular manifestations, demyelinating disease, or immune-mediated encephalitis. GvHD could be prevented or treated with immunosuppressant such as corticosteroids, but CNS-related GvHD after allo-HSCT is associated with a poor prognosis.

GIDs could be serious side effects after transplantation of fetal VM tissue for PD patients. Clinical pattern and risk factors for dyskinesias following fetal nigral transplantation in PD have been investigated [63]. On-medication dyskinesias are typically generalized and choreiform. In contrast, off-medication dyskinesias are usually repetitive, stereotypic movements in the lower extremities with residual Parkinsonism in other body regions. Off-medication dyskinesias are common following transplantation and may represent a prolonged form of diphasic dyskinesias which are associated with partial or incomplete dopaminergic reinnervation of the striatum [63]. The pathophysiological mechanism underlying GIDs can be partially attributed to excessive serotonergic innervation in the grafted striatum of patients who developed off-medication dyskinesias later following the initial improvement of motor symptoms after transplantation. It has been realized that the dyskinesias can be markedly attenuated by systemic administration of a serotonin [5-hydroxytryptamine (5-HT)] receptor (5-HT1A) agonist [64]. A recent study demonstrated a mechanistic link between serotonin 5-HT6 receptor or a cyclic adenosine monophosphate (cAMP)-linked designer receptors exclusively activated by designer drugs (DREADD), intracellular cAMP, and GIDs since exclusive activation of serotonin 5-HT6 receptor, located on the grafted DA neurons, is sufficient to induce GIDs [65]. GIDs resulting from cell therapies for PD with fetal tissue or stem cells are therefore possibly avoided and treated with serotonin receptor agonists.

The TRNSEURO (NCT01898390), a multicenter European initiative on PD transplantation using fetal VM tissue, has been conducted since 2012, in an attempt to overcome obstacles such as inconsistent methods between the previous trials [66]. The issues on administration of

immunosuppressant and anticonvulsant, the method of graft preparation, and the precise site of graft placement will be further resolved. However, heterogeneous compositions of the graft, difficulties in standardization of cellular material, and ethical concerns are limitations in these trials using fetal VM tissue. In addition, complications associated with procedures of transplantation, such as subdural hematoma, have to be prevented [59].

NSCs preserve the ability to self-renew and differentiate into all neural lineage cells, including neurons, astrocytes, and oligodendrocytes, and they are therefore a source of potential graft for cellular transplantation in neurological disorders. Together with ECs and pericytes, NSC can constitute the functional NVU for tissue restoration in PD. Since neurons are integrated into the neurovascular network with other cellular and acellular compositions in the NVU, combined transplantation of NSCs with other types of cells or biomaterials may be more efficacious for tissue replacement. Local factors within the microenvironment of transplanted NSCs affect the fate of the cells, as measured by survival, proliferation, differentiation, and neurogenesis [67]. Several groups have studied modulation of stem cells or DA cells with combined cellular transplantation in animal models of PD (**Table 1**) [68]. Besides the attempt to replace damaged tissues, it was shown that grafted cells may promote endogenous vasculogenesis and neurogenesis in the neighboring tissues [69].

To administer cell transplantation therapies, NSCs can be delivered transcranially through the needle into deep targets, such as putamen for PD. This approach minimizes the problem that BBB could be a barrier preventing intravascularly transplanted cells from crossing the vessel wall into brain tissue [70]. It has been proposed that 100,000 surviving DA neurons per

Type of transplanted cells		Animal model	Significance	Ref.
Mouse fetal DA neurons	Mouse mesencephalic NSCs overexpressing human glial-derived neurotrophic factor (GDNF-mNSCs)	6-OHDA rat	Apomorphine-induced rotation was reduced by co-transplantation of fetal DA neurons with mNSCs genetically modified to overexpress GDNF, which supports differentiation into DA cells and their survival.	[72]
Human embryonic NSC	Macaque autologous Schwann cells (SCs)	6-OHDA macaque	Gomez-Mancilla dyskinesia score in the group of co-transplantation with SCs and NSCs was significantly lower than the control group. SCs harvested from the autologous peripheral nerves can avoid rejection.	[89]
Human umbilical cord-derived MSCs	Human dermal fibroblasts	MPTP rat	Fibroblasts may be common cell contaminants affecting purity of MSC preparations and clinical outcome in stem cell therapy protocols.	[90]
Rat embryonic DA neurons	Rat Schwann cells (SCs) overexpressing basic fibroblast growth factor (FGF-2)	6-OHDA rat	Co-transplantation of DA neurons and FGF-2 overexpressing SCs differentially affects survival and reinnervation. Behavioral recovery underlines the necessity of direct contact between FGF-2 and DA neurons.	[91]

Table 1. Modulation of stem cells or dopaminergic (DA) cells with combined cellular transplantation in PD (adopted from "Potential of Neural Stem Cell-Based Therapy for Parkinson's Disease" [68]).

putamen is the minimum required for a successful outcome following intracranial transplantation [71]. Bilateral injection targeting putamen is favored more than unilateral transplantation although there seems to be no consensus yet.

It is reasonable to optimize the microenvironment surrounding the transplanted NSCs or DA neurons in order to support differentiation into DA cells and their survival *in vivo*. A recent study demonstrates that co-transplantation of fetal DA neurons with mouse NSCs, genetically modified to overexpress human glial-derived neurotrophic factor (GDNF), mitigates motor symptoms in a rat model of PD [72]. To optimize survival and guide appropriate differentiation of grafted NSCs, ECs have been combined with NSCs for transplantation into animal brains with stroke but not yet in brains with PD [73].

6. Application of stem cells in Parkinson's disease

Technically DA neurons could be derived from embryonic stem cells (ESCs), mesenchymal stem cells (MSCs), umbilical cord blood hematopoietic stem cells (HSCs), and induced-pluripotent stem cells (iPSCs) generated from adult somatic cells, as well as directly from NSCs [74]. Several factors including the long-term survival and phenotype stability of stem cell-derived neurons or glial cells in the graft following transplantation, the purity of populations of cells derived from NSCs, and safety issues related to the risk of tumorigenesis have to be evaluated in greater depth [75]. An appropriate cell culture model for investigating, paracrine, autocrine, and juxtacrine signaling pathways within the neurovascular environment can provide a platform for characterizing cells with various origins and for selecting the optimal cells for transplantation [76].

NSCs derived from the whole ganglionic eminence and the ventral mesencephalon region of human fetuses have been immortalized using the technique of c-mycER transduction, and these NSC lines have been induced and differentiated to neurons potentially producing tyrosine hydroxylase (TH), a critical enzyme involved in dopamine synthesis [77, 78]. A recently devised cell culture model combined human adult brain ECs with fetal-derived NSCs which retain the ability of differentiating and further integrate together with ECs into the neurovascular tissue [79]. In this system, a distinctive neurovascular cytoarchitecture comprised of NSCs and ECs was observed. It simulates several features of the neurovascular niche, such as diffusible proteins, an extensive matrix, and expression of receptors, and genes unique to each cell type [76]. Moreover, complex multi-stage angiogenic processes can be studied by modulating the contact and soluble factor-mediated signaling pathways [76]. Studies using this NVU model will promote the best regimen for NSC-based therapies in PD [80].

Appropriate cell-to-matrix interactions are required for neurovascular tissue regeneration by NSCs and ECs. It is therefore important to investigate contact-dependent factors, including ECM components which are involved in NSC-mediated endothelial morphogenesis and vasculature shaping. ECM molecules are differentially expressed within the NVU [76] and they may have inhibitory and excitatory bioactivities. Astrocyte-derived thrombospondins, for example, have been shown to induce presynaptic differentiation in the CNS [81], but

conversely, thrombospondin-1 functions as a negative regulator of angiogenesis [82]. The functions of these ECM molecules are associated with expression of their respective receptors, such as integrins. Most integrins recognize several ECM molecules, and most matrix molecules bind to more than one integrin. Consequently, various ECM molecules compete to bind specific integrins [83]. When studying neurovascular regeneration for NSC-based therapies in PD, an ideal *in vitro* NVU model should provide a system for investigating not only intercellular, but also cell-to-matrix interactions [76, 79].

7. Perspectives on the neural stem cell-based therapy for Parkinson's disease

Researches on pathophysiology of PD and establishment of valid and effective NSC lines will benefit from development of advanced cell culture models of the NVU. Patients with PD will have the opportunity to be treated with the cells if DA neuronal differentiation can be guided appropriately. Preclinical studies on image-guided injection and noninvasive monitoring of tissue regeneration in animal models of PD will provide the optimal therapeutic window, cell dose, and delivery route for cell transplantation [80]. Finally, appropriate patient selection and clinical follow-ups are required as a precondition for successful clinical translation of NSC-based therapies.

Recently, a preclinical study using a primate model suggests that human iPSC-derived DA progenitors are clinically applicable for the treatment of patients with PD. It was demonstrated that human iPSC-derived DA progenitor cells survived and functioned as midbrain DA neurons in a primate model of PD (*Macacafascicularis*) treated with the neurotoxin MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) [84]. The therapeutic effect was consistent regardless of the origins of the cells either derived from PD patients or healthy individuals, and there was no tumor found in the brains for 2 years.

Alternatively, using parthenogenetic stem cells as a source of donor tissue have raised hopes for PD patients [85]. The parthenogenetic cells are derived from unfertilized oocytes through suppression of the second meiotic division, leading to a pluripotent diploid cell line containing exclusively maternal chromosomes [86]. They are therefore different from other pluripotent cell sources such as ESCs or iPSCs and may overcome obstacles such as the possibility of tumorigenesis. However, their lack of paternal imprinting may be associated with unique challenges in their adoption clinically as this could affect their cell cycle and differentiation capacity [87]. Notably, preparation of these cells and the transplantation procedure has to be produced under Good Manufacturing Practice (GMP) conditions, the established guidelines and safety regulations [88].

In conclusion, combined with cutting-edge technologies, including cellular reprogramming, advancement in scaffolds for brain tissue engineering, image-guided injection, and noninvasive monitoring of tissue regeneration, NSC-based therapies will alleviate symptoms of PD patients in upcoming clinical trials of cell replacement therapy once the implanted or regenerated DA neurons are integrated into the existing nigrostriatal DA pathway.

Acknowledgements

Preparation of this article was supported by the Ministry of Science and Technology Taiwan, the Republic of China (104-2314-B-016-017-MY3) and Tri-Service General Hospital, National Defense Medical Center (TSGH-C105-085, TSGH-C107-007-007-S05, MAB-106-041, MAB-106-042, and MAB-106-044). The funder had no role in the decision to publish or in manuscript preparation.

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Chapter 6

Mucuna and Parkinson's Disease: Treatment with Natural Levodopa

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.74062

Abstract

Mucuna pruriens is a tropical bean containing large amounts of levodopa and is the most important natural remedy for Parkinson's disease. Famous neurologists have patented methods of extraction for its advantages over the synthetic forms, Sinemet and Madopar. This natural levodopa is less toxic and has a faster and more lasting effect and can delay the need for pharmaceuticals and combination therapies. Currently, there are many patients with Parkinson's disease who take *Mucuna* and spontaneously reduce the dose of conventional drugs and do so behind their doctors' backs. *Mucuna* should always be taken under medical supervision.

Keywords: *Mucuna pruriens*, Parkinson's disease, levodopa, natural, treatment, benefit, dyskinesia, conventional

1. Introduction

Mucuna pruriens is a species of bean that grows in the tropics. It is very rich in natural levodopa, which is better tolerated and more potent than the synthetic levodopa in Sinemet, Madopar, or Stalevo. *Mucuna* seed extract has been an effective treatment of Parkinson's disease (PD) in many patients. Scientific studies attest to it, and renowned neurologists have patented the specific techniques for extracting levodopa from this plant. They *relate to the use of Mucuna pruriens seeds for the preparation of a pharmaceutical composition for the treatment of Parkinson's disease to obtain a broader therapeutic window in L-Dopa therapy, to delay a need for combination therapy, to obtain an earlier onset and longer duration of L-Dopa efficacy, and to prevent or alleviate acute and chronic L-Dopa toxicity* [3, 44]."

Meanwhile, patients have recorded their positive experiences with *Mucuna*; they buy it online (no prescription needed) and use it in secrecy without consulting their neurologist. It is used without control, and if there are not more accidents, it is because it is relatively safe (although there are risks if misused), and most of the capsules sold contain very low doses, almost like a diet supplement. The formula at high concentrations is dangerous, especially when mixed with antiparkinsonian drugs. Neither the patients nor the doctors (most of them) have clear ideas about this plant, its ingredients (not only levodopa), the proportions in which it is absorbed, or how to manage it.

2. *Mucuna pruriens*: the plant

Mucuna pruriens is a kind of "hairy" or furry bean, native to Southeast Asia, especially the plains of India, but also widely distributed in tropical regions of Africa and the Americas (particularly in the Caribbean). The wide dissemination of the plant explains its variety of names, depending on the location: velvet beans, cowhage, itch bean, picapica, Fogareté, Kapikachu, sea bean, deer eyes, yerepe, Atmagupta, nescafe, and chiporazo. *Mucuna* is a legume (such as common beans, peas, lentils, peanuts) and the largest natural source of levodopa.

This annual plant grows as a climbing shrub with long tendrils that enable it to reach more than 15 feet in height. Young plants are almost completely covered by a diffuse orange hair that disappears as they age. It grows or is cultivated as fodder to enrich the soil (adding a lot of nitrogen) or for its medicinal qualities.

Mucuna is called "pruriens" because of the intense itching produced by their contact. The orange "hairs" of flowers and pods of *Mucuna pruriens* contain chemicals (including serotonin) that, when they come in contact with the skin, cause intense irritation and itching and sometimes very troublesome injury including allergies and severe swelling.

In India, *Mucuna* has been the main healing herb for three thousand years. All parts of the plant are used in more than 200 indigenous medicinal preparations. The seeds contain up to 7% levodopa, which is used in the treatment of Parkinson's disease. In the Ayurvedic medicine, velvet bean is recommended as an aphrodisiac, and studies have shown that its use causes a rise in testosterone levels, increased muscle mass and strength, and also improves coordination and attention.

Extract of *Mucuna* seed powder contains large amounts of levodopa and a little serotonin and nicotine along with other ingredients that are only partially known. In the treatment of Parkinson's disease, such extracts seem to be more effective and less toxic than the synthetic preparations [1].

3. *Mucuna*: therapeutic possibilities

The interest in *Mucuna* increased after 1937 when it was discovered that the variant contained large amounts of levodopa. However, this amino acid alone does not justify the many medical applications of this interesting plant.

In the treatment of Parkinson's disease, some results in groups of patients and in experimental animals show that, apart from natural levodopa, *Mucuna pruriens* has other ingredients that show outstanding features. It must contain other substances that improve the absorption of levodopa and metabolic efficiency, as explained below.

To date, 50 substances have been identified in the powder of its seeds [2]. Other still unidentified components must exist in *Mucuna*, such as portions or mixtures of alkaloids, proteins, peptides, polysaccharides, glycosides, glycoproteins, and several phytochemicals including tryptamine, alanine, arginine, glutathione, isoquinolone, mucunine, nicotine, prurienine, serotonin, tyrosine, etc., [3].

These substances, identified or not, confer special powers on *Mucuna*, perhaps boosting the levodopa or adding some kind of dopamine agonism and even extended its effects. We need to continue investigating them.

3.1. Strategies to enhance levodopa

Trials have been conducted in which *Mucuna* seeds are germinated in darkness or in different conditions of light and providing varied nutrients (oregano, proteins from fish, etc.). Results showed that by adding oregano to seeds germinated in darkness, *Mucuna* sprouts containing 33% more levodopa have been obtained [4]. Other researchers selected some cells from the ground and then grew them grow in a medium that allows nutrients to be supplied; in this way they have managed successfully to increase the concentration of levodopa [5, 6].

3.2. Beneficial effects of *Mucuna*

Mucuna is recommended in Ayurveda to treat more than 200 diseases—as a vital tonic, an aphrodisiac, a remedy to reduce stress, a good diuretic, etc.—and is also used against parasites, to control diabetes and lower cholesterol. And, of course, it is a treatment for *kampavata* (the equivalent of Parkinson's disease). Western science seems to confirm many of these effects. *Mucuna* improves libido, semen quality, etc., and even works against snake bites.

Mucuna increases the adaptation and regeneration of tissues in general and has been shown to increase growth hormone [7]. It has an anabolic effect and increases muscle mass; it also has antioxidant properties and favors the protective functions of the liver [8].

Diabetics and people with high cholesterol may benefit from *Mucuna* [9]. In rats it has been shown to lower cholesterol by 61%, and glucose was reduced by 39% [10]. *Mucuna* enhances the recovery of diabetic neuropathy induced in animals [11]. In humans it delays the onset of diabetic nephropathy.

Mucuna also protects the stomach to relieve gastric mucosal lesions induced experimentally in rats [12]. *Mucuna* contains prurienine which increases intestinal peristalsis and is a good remedy for constipation, so prevalent in Parkinson's disease patients. It usually enhances motility and gastric emptying, although some patients assert otherwise.

3.3. Aphrodisiac and antiepileptic

Mucuna increases libido, or sexual drive, in men and women due to its dopamine-inducing properties; dopamine is the substance of desire and profoundly influences all appetites. In

male animals *Mucuna* raises testosterone levels and increases sexual activity [13]. In men with fertility problems, *Mucuna* clearly enhances sexual drive and power while improving the quality of the sperm: it increases the number of cells and also gives them greater mobility [14]. It is assumed that it acts on the hypothalamus-pituitary-gonadal axis.

Researchers can cause status epilepticus or catalepsy in experimental animals by various techniques: electroshock, pilocarpine, or Haloperidol. These improve if treated with velvet beans [15].

3.4. Snake poison antidote

This is not an exaggeration or a myth. *Mucuna* is a good antidote for snake bites, possibly by a direct effect on the venom, attributed to its glycoprotein antitrypsin content [16] but also because it is procoagulant and prevents cardiorespiratory depression induced by poison.

Specifically, *Mucuna* reduces mortality due to bites from the following snakes: Gariba viper (*Echis carinatus*), Viper Malaya, and spitting cobra (*Naja sputatrix*) [17].

3.5. Kampavata is Parkinson's disease

In India there were Parkinson's disease patients three thousand years before the birth of James Parkinson. These were diagnosed as *Kampavata*, a disease characterized by trembling (*Kampa* in Sanskrit). In Ayurveda this process was classified within the group of neurological disorders (*Vata Rogas*) [18, 19].

They obviously lacked Sinemet and Madopar but were treated naturally with levodopa, obtained by crushing *Mucuna* seeds, which they later diluted and administered as a beverage [20]. For thousands of years; this therapy has worked, these patients have improved and, above all, according to that we know, showed fewer side effects than people taking synthetic drugs.

3.6. The seeds are cooked in cow's milk

In an interesting clinical trial, 18 Parkinson's disease patients were treated according to the criteria of Ayurvedic medicine. They received a concoction of powder of *Mucuna pruriens* cooked in cow's milk along with other traditional plants (*Hyoscyamus reticulatus, Withania somnifera, Sida cordifolia*) [21].

The results found that this treatment improved rigidity and bradykinesia; tremor was diminished and cramps subsided; however, sialorrhea (drooling or excessive salivation) worsened. Later, the powder of plants which had been added to the milk was analyzed, and it was found that each dose used contains 200 mg of levodopa [21].

The Hindu *Mucuna* extract contains a small amount of levodopa that fails to justify the significant clinical improvement of parkinsonian symptoms. This suggests that in the *Mucuna*, there are other substances that enhance the role of levodopa (such as carbidopa, entacapone, or tolcapone) or other active ingredients with antiparkinsonian effects [20, 22, 23].

One important thing is guaranteed by Ayurveda: after thousands of years of using these plant extracts, thousands or millions of patients have continued to improve their symptoms without significant adverse effects.

4. *Mucuna* works better than Sinemet

In 1978, a publication by R.A. Vaidya in India stated that Parkinson's disease could be treated with extracts of a plant, *Mucuna pruriens*, which contains natural levodopa and is tolerated better than the synthetic version [24]. In the West the scientific writings that described improvement in parkinsonian symptoms after eating *Mucuna* or other beans appear between 1990 and 1994 [18, 25, 26]. These legumes could replace some of the conventional medications. There are some recipes from "Parkinsonian cuisine" that are based on beans [22, 27].

4.1. *Mucuna* seed powder

Scientific journals have begun publishing cases of improvement in patients after eating *Mucuna*. The Parkinson's Disease Study Group undertook a multicenter clinical study (in collaboration with several hospitals) with 60 patients, of which 26 took Sinemet before the test and the other 34 were "pharmacologically virgins" (they had never taken levodopa). All were treated for 12 weeks with powder from *Mucuna* seeds: an average of six bags, each containing 7.5 grams, equivalent to 250 mg of levodopa. In other words, each sachet contained the same amount of levodopa as a Sinemet 25/250 but without the carbidopa. Neurologists of four centers screened patients using the appropriate scales (UPDRS) and found considerable improvement that was statistically confirmed [28]. Thus, Ayurveda medicinal recipes have demonstrated their clinical effectiveness.

4.2. Zandopa: a medicine with *Mucuna*

This legume seems to work. Investigations gave evidence of this, and *Mucuna* seed powder (called HP-200) was marketed as a drug, under the brand name Zandopa [2]. It was first distributed in India and has been available in the United Kingdom since 2008. Now customers can buy it freely online without a prescription. It is important to be careful, however, because the levodopa dose is relatively high (250 mg per sachet) when combined with carbidopa or other antiparkinsonian drugs.

4.3. Improvement in mice doubles or triples

We can experimentally induce parkinsonism (unilateral or bilateral) in rodents via certain toxic substances. Used in these trials, levodopa from *Mucuna* has no side effects and produces an improvement that is double or triple that of the synthetic version [29].

In another experiment, animals ate extract of *Mucuna* for a year. They were then put down, and their neurotransmitters were measured in different areas of their brains. Interestingly, no changes were seen in the nigrostriatal pathway, but dopamine was significantly increased in the cerebral cortex [2]. This has two possible explanations: that natural levodopa is more potent or that *Mucuna* contains other beneficial chemicals.

4.4. Improvement in humans

This clinical study [1] complies with the strict requirements laid down by the most rigorous scientific methodology established by the Quality Committee of the American Academy of

Neurology [30]. This was a randomized, double-blind, crossover study which adhered to precise objectives and clearly defined protocols and was carried out by several independent observers.

They studied eight Parkinson's disease patients at (on average) 62 years of age, 12 years after diagnosis with a stage of progression of 3.5 on the Hoehn and Yahr scale. Prior to this test, they were treated with levodopa (572 mg mean value). In addition, patients were taking other previous associated drugs (amantadine, pergolide, ropinirole, pramipexole, or cabergoline) that remain unchanged. All had a rapid response to levodopa (1.5 to 4 hours) along with very disabling motor fluctuations during the morning.

Each subject was hospitalized three times (1 week apart) and went without any medication the night before the test. The next morning, at the same time, each received at random one of three combinations: one dose of 200 mg of levodopa with 50 mg of carbidopa (two tablets of Sinemet Plus) or two or four sachets of *Mucuna* (15 or 30 grams) equivalent to 500 or 1000 mg of natural levodopa (100 or 200 according to the conversion factors).

The results were clearly better in those who take two sachets of *Mucuna* extract: improvement in their symptoms occurred faster, their plasma levodopa levels were higher, and clinical efficacy was more durable. In addition, their dyskinesia was not worsened. The details follow.

4.5. "Citius, altius, fortius et durabilius"

The Olympic motto *faster, higher, stronger* can be applied to *Mucuna*, because, in comparison to Sinemet, it acts more rapidly (34 minutes instead of 68), produces a greater elevation of the plasma level of levodopa (110% higher), and appears to be stronger (the effectiveness of natural levodopa is double or triple that of the synthetic version). In addition, the improvement achieved is more durable (with *Mucuna* the "on" phase is prolonged 37 minutes longer than with Sinemet). Therefore, it can be described as *citius, altius, fortius… durabilius*.

4.6. Twice as effective

We have seen that the *Mucuna* seed extract naturally contains levodopa. If we quantify and compare it to the same dose of synthetic levodopa contained in tablets of Sinemet (or Madopar), we find that levodopa from *Mucuna* is approximately twice as powerful in controlling parkinsonian symptoms [31].

The efficacy of synthetic levodopa (without carbidopa) has been compared to that of natural levodopa (*Mucuna*) using rats with experimentally induced parkinsonism. The natural levodopa proved to be two times as effective at improving symptoms [32]. This test maintained the following proportions: 125 and 250 milligrams of synthetic levodopa were compared with the equivalent dose of natural levodopa (respectively, 2.5 and 5 grams of *Mucuna* powder 5%). Then the test was repeated, this time adding 50 mg of carbidopa to the two types of levodopa. Again, *Mucuna* proved to be more efficient.

4.7. The problem of volume

Mucuna is more effective, more rapid, and durable; however, to achieve a dose that will offer the same relief as Sinemet or Madopar, it would be necessary to prescribe large amounts of

seed powder dissolved in liquid [24, 33]. The need to consume seed powder several times a day would soon overwhelm the patient, and the treatment would be abandoned as too cumbersome.

The solution to the problem can be found in concentrated extracts. This allows for the presentation of *Mucuna* in tablets or capsules, facilitating the application of different doses of the product and making it easy to manage daily consumption of *Mucuna* in the amounts deemed necessary. There is another choice that requires the cooperation of the neurologist: *Mucuna* could be used in association with carbidopa to achieve greater efficiency with less seed powder.

4.8. *Mucuna* with carbidopa

The first trials that compared the effects of Sinemet with *Mucuna* required six or seven daily sachets of powdered seeds. This can be maintained for a few days but becomes quite cumbersome with time. Actually those studies were done to compare natural levodopa (*Mucuna*) to a synthetic combination of levodopa and carbidopa (i.e., the contents of Sinemet).

The solution seems simple: add carbidopa to *Mucuna*. This increases the efficiency of the natural levodopa contained therein and therefore eliminates the need to take large amounts of seed powder. We must be careful when capsules of concentrated extracts are used because the dose can be excessive when you consider that *Mucuna* is more effective than synthetic levodopa.

There are published trials in which *Mucuna* is administered in combination with carbidopa and is compared to Sinemet. Rats with experimentally induced hemi-parkinsonism were treated with powdered *Mucuna* seeds (2.5 and 5 g) associated with carbidopa (50 mg) and in contrast to other groups wherein the equivalent synthetic levodopa dose (125 and 250 mg) was also associated with carbidopa. *Mucuna*-carbidopa proved to be more than twice as effective as Sinemet, and this was found by measuring the rotation contralateral (on the injured side) of the animals in each group [32].

Very recently, a new trial was performed to investigate whether *Mucuna pruriens* (MP) may be used as alternative source of levodopa for indigent individuals with Parkinson's disease (PD) who cannot afford long-term therapy with marketed levodopa preparations. Eighteen patients were included in a double-blind, randomized, controlled, crossover study [34]. It shows that single-dose *Mucuna pruriens* intake met all noninferiority efficacy and safety outcome measures in comparison to dispersible levodopa/benserazide. Clinical effects of high-dose MP were similar to levodopa alone at the same dose, with a more favorable tolerability profile [34].

We know that the carbidopa in Sinemet prevents the peripheral side effects of levodopa (nausea, rapid heart rate) and enhances mobility. It appears that the carbidopa in *Mucuna* is even more effective: it decreases mild side effects and doubles or triples patients' strength [1].

4.9. Other advantages of *Mucuna*

Mucuna does not produce dyskinesia. A different study, this time in monkeys (with unilateral parkinsonism induced experimentally), produced very interesting results on the possibility of dyskinesias. One group was treated with Sinemet (levodopa and carbidopa), another with *Mucuna* plus carbidopa, and the third only with *Mucuna*. All the animals experienced an improvement in their symptoms. Dyskinesia was then assessed by the study of spontaneous activity in the substantia nigra. Larger dyskinesia appeared in the Sinemet group. In those

treated with the combination of *Mucuna* and carbidopa, dyskinesia seemed more moderate. Interestingly, in those who had only taken *Mucuna*, no dyskinesia was found [35].

Long-term Mucuna without dyskinesia. A similar experiment was performed, but this time *Mucuna* treatment was continuous, extending for a year. It was done in rodents and compared *Mucuna* with Madopar. One group was treated with Madopar (levodopa and benserazide), another with *Mucuna* plus benserazide, and the third only with *Mucuna*. All were controlled for a year. The symptoms were alleviated in all groups, but the improvement was significantly higher in those who were treated with *Mucuna* plus benserazide.

To highlight the results of long-term use: after 1 year, major dyskinesia appeared in rats that had taken Madopar. Rodents treated with *Mucuna* plus benserazide had some minor dyskinesia while for animals that took only *Mucuna*, none at all [36]. Even more, in an experiment with different dyskinesias (those produced by neuroleptics like haloperidol), these repetitive movements improved when *Mucuna* was administered [37].

Mucuna is neuroprotective. It seems that natural levodopa from *Mucuna* (or the whole of the components in this legume) is nontoxic and even neuroprotective [38]. This has been demonstrated in mice (with experimentally induced parkinsonism) which were given synthetic levodopa or *Mucuna*. Those treated with *Mucuna* experienced an improvement in most of the symptoms. Also, when they were slaughtered 1 year later for brain analysis, it was found that the endogenous contents of levodopa, dopamine, norepinephrine, and serotonin in the *substantia nigra* were significantly restored [2].

In other studies with rodents, researchers agree that the extract of *Mucuna* clearly is neuroprotective compared to synthetic levodopa [39] or estrogen [40]. They believe that this is due to its antioxidant and chelating activity (processing of iron) and because it avoids mutagenic effects in DNA [41, 42].

Antioxidant and neuroprotective properties of *Mucuna* have also been shown in rodents that were previously damaged experimentally by nerve toxins such as paraquat. The results also highlighted the improvement in habits and cognitive functions of these animals [43].

Dosage does not increase over time! It sounds too good to be true: treatment with *Mucuna* does not produce dyskinesia; and it also improves secondary abnormal movements which occur with chronic synthetic levodopa therapy. One more thing, with *Mucuna* it would be not necessary to gradually increase the dose as time goes on, as is the case with those taking synthetic drugs.

Below, I transcribe literally the benefits of *Mucuna* extracts as reflected in the scientific foundations of the patent carried out by Van der Giessen, Olanow, Lees, and Wagner [3]: "Conventional L-Dopa therapy requires a gradual increase of the effective dose over time resulting of progression of disease and/or the neurotoxic effects of L-Dopa or dopamine with an increase of toxic reactions and, over time, the appearance of dyskinesia, increasing in severity with dose. In clinical experiences with *Mucuna pruriens* seed preparations, these negative phenomena have not been observed in that for the effective treatment of Parkinson's, the *dose of Mucuna pruriens derived L-Dopa remained relatively stable over longer periods of time, and in that dyskinesia, even in patients with pre-existing dyskinesia following long term therapy with conventional L-Dopa* preparations, appeared to be less in occurrence and severity…" [3].

After reading this, it seems strange that *Mucuna* is not yet dispensed in all pharmacies as a revolutionary drug.

4.10. atents of extracts of *Mucuna*

The proprietaries over certain techniques of *Mucuna* extracts—WO 2004039385-A2 [44] and US 7470441-B2 [3]—are very prestigious researchers. They have developed specific techniques to extract various substances from *Mucuna*, not only levodopa. As they have detailed, many of the ingredients are indicated "…for preventing, alleviating or treating neurological diseases," for general use as "a pharmaceutical combination for neuroprotection or neurostimulation," and, more specifically, "for the treatment of Parkinson's disease." They have left little to no chance.

4.11. Zandopa and a cocktail with *Mucuna*

The previously mentioned Zandopa brand from Zandu Laboratories, which owns the patent for *Mucuna* powder product known as HP-200, was used in important clinical trials [28, 45] and has been marketed for several years. Som C. Pruthi has patented [46] a combination from the Ayurveda tradition that mainly contains *Mucuna* (between 55 and 99%), together with *Piper longum* and *Zingiber officinale*. He described a woman diagnosed with Parkinson's disease at age 51 that did not tolerate conventional medicines. She took Pruthi's combination of *Mucuna* for 12 years. In this long period, it was found that progression of the disease was very slow and side effects were not detected.

4.12. An extra-concentrated extract

The drawback of *Mucuna* powder and primitive extracts is the large volume of legume one needs to consume in order to achieve sufficient blood levels of levodopa. This produces overeating and gastrointestinal upset and causes many to abandon this therapy. To avoid this trouble, Manyam has patented a method [47] involving the removal of grease from the cotyledons of the seeds. Using ethanol as a solvent, the concentrated extract is isolated and finally freeze-dried.

With this technique, it is possible to process 2.5 kilograms (over 5 pounds) of *Mucuna* powder, which is then reduced to just 46 grams (1.6 ounces). In this conversion the relative proportions of levodopa are maintained (or even increased). So the amount of vegetable to be ingested is reduced to less than 2%. In this way, it can be supplied as tablets, capsules, or syrup and even diluted for injection [47]. On the other hand, its efficacy has been demonstrated in vitro and in animals: when this concentrated extract is supplied to rats with "induced parkinsonism," their symptoms improve twice as much as the treatment with synthetic levodopa [32].

4.13. More benefits than conventional levodopa

The foundations of the patent, based on the references provided, reveal that, in relation to standard levodopa-carbidopa medications (Sinemet) or levodopa-benserazide (Madopar), the extracts of *Mucuna* have important advantages that confirm those listed in the previous chapter.

Mucuna has a wider therapeutic window: the range of dosage in which a drug can be used without causing toxic effects. That means that there is a large margin between the minimally effective dose of *Mucuna* and one that could cause damage in the body.

Patients get better sooner with it. Researchers gave patients a tablet of Sinemet, and they noticed the "on" effect after 54 minutes. But when they took *Mucuna*, they were already active after only 23–27 minutes [1]. In addition to being quick-acting, *Mucuna* (at a dose of 30 grams) has been found to be effective for longer durations: patients were still "on" for 204 minutes after taking the seed extract, beating Sinemet tablet by half an hour [1].

Neither acute nor chronic toxic effects have been described. Even with high doses of *Mucuna*, there were less adverse effects (nausea, abdominal discomfort) than in patients who received the equivalent of the conventional drugs [3]. Other long-term studies of *Mucuna* (in monkeys and rats) have shown that the dreaded dyskinesia and other symptoms associated with continuous treatment with levodopa are lower and in some cases even tend to improve [35, 36].

4.14. Other benefits of *Mucuna*

According to the application for the patent, *Mucuna* alone may suffice to relieve patients' symptoms for a period of time, and therefore combination therapy (levodopa plus agonists) can be delayed. Even more, these renowned specialists believe that *Mucuna* extracts may be useful in the treatment of multiple neurodegenerative processes: chorea, Parkinson's and Alzheimer's diseases, and vascular dementia [3]; further applications include many other metabolic disnutritional disorders and, systemic, endocrine and autoimmune disturbances (vitamin deficiency, lupus, demyelinating, etc.), as well as neurotoxic, ischemic, or traumatic injuries [44].

Anecdotally, a woman with white hair has been described that after 3 months of treatment with *Mucuna*, it turned back to black [50], "like when I was young," she said. This is food for thought: the threads connecting youth, dopamine, suffering, old age, stress, and gray hair [48, 49].

4.15. *Mucuna* is more than levodopa

The available data has shown that *Mucuna pruriens* has special properties that distinguish it from synthetic levodopa. These data provide a basis for the patent registered by Olanow and Lees (quoted *verbatim*): "the *M*ucuna pruriens formulation seems to possess potential advantages over existing commercially available synthetic L-Dopa formulations in that it combines a rapid onset of action with a comparable or longer duration of therapeutic response without increasing dyskinesias or acute LD toxicity in spite of much higher LD plasma levels…" [3].

Natural ingredients (known or unknown) combined with levodopa may contribute to improvement of parkinsonian symptoms and reduction of dyskinesia [44]. This opens up the anticipation of important therapeutic progress and the hope of further studies to confirm that extracts of *Mucuna* seeds are a safe and effective alternative [35]. Currently, patients who are using *Mucuna* under medical advice generally report a lowering of their doses of conventional drugs, and fewer side effects, in both the short and long terms.

http://dx.doi.org/10.5772/intechopen.74062

5. Contraindications and warnings

Mucuna has some drawbacks. In principle, the levodopa itself (albeit with other natural ingredients that improve tolerance) shares many of the contraindications and precautions applicable to synthetic levodopa. These warnings are well known, and we will review some of them.

I want to begin by highlighting the main stumbling block to the beneficial use of *Mucuna*: ignorance on the part of the patient and lack of medical information. A physician should monitor treatment at all times.

5.1. Patients do not know what they are taking

A major obstacle to treatment with *Mucuna* is that patients don't have clear ideas about the drugs' intended purpose. They have heard of several cases where *Mucuna* worked well, but usually these observations have come to them from people without any scientific knowledge, from nonprofessional websites or from commercial information intended for product sales.

Mucuna is sold freely on the Internet, and many patients take it without medical supervision. Worse still, they engage in speculation based on bizarre opinions they encounter in the forums, and they absorb this erroneous information and therefore lack sufficient knowledge to use it appropriately. However, occasionally patients are right or are very close to the truth, but there is still a danger of misuse. At times patients take *Mucuna* simply because despair leads them to try anything.

5.2. Most doctors are skeptics

Many patients complain of the disdainful reaction they encounter when they ask their doctors about adding *Mucuna* to their treatment regimen. As it is an "unorthodox" therapy, it is perfectly understandable that the physician does not want to prescribe *Mucuna*: it is not part of the generally accepted body of treatments they are trained to manage. When a doctor decides to incorporate *Mucuna*, he faces new difficulties, particularly with patients treated with other drugs. This requires the additional effort of studying the situation and designing a strategy for each individual case.

On the other hand, we cannot allow patients to treat themselves in hiding. Therefore, it is desirable that as doctors, we have to educate ourselves about *Mucuna* so that we can choose to use it or not in a particular type of patient. One should never despise the unfamiliar. After studying the properties of *Mucuna* and weighing its advantages and disadvantages, we should decide on a rational basis whether it is beneficial, neutral, or inadvisable for a specific case.

If the patient perceives that we master the subject, he will entrust his care to us, rather than attempting to treat himself. That way, he will cooperate if we ban the *Mucuna* or recommend a gradual dosage pattern. We earn their trust when we have enough information and credibility.

5.3. Why are there no frequent major problems?

Mucuna is not a placebo but, rather, has important effects. However anyone can buy it without a prescription, and most are taking it without medical supervision. These patients are not sufficiently familiar with the properties of *Mucuna*; they do not know the side effects or complications that may arise; they do not take into account the interactions with other medications or the differences between individuals.

While this scenario suggests a public health issue, it fortunately does not usually cause serious problems. Why? I think that one reason is the safety of the components of *Mucuna*, which has been used for millennia in thousands or hundreds of thousands of patients in India without significant harmful effects. Another issue is that the products are sold often in small doses as a dietary supplement. That is not, however, always the case: there are some preparations with excessive doses especially when combined with carbidopa (in Sinemet, Madopar, or Stalevo), dopamine agonists, or other antiparkinsonian drugs. It is necessary to use extreme caution.

5.4. Contraindications of levodopa

Although better tolerated, *Mucuna* contains a natural form of levodopa. In theory it should share the same contraindications, interactions, and precautions of synthetic levodopa: It is contraindicated in children, pregnancy, and lactation (prolactin inhibition) and schizophrenia or psychosis. It should be used with caution (and is best avoided) in cases of a medium to severe degree of heart disease or diabetes. Do not take it with MAOIs or with ergot. Use caution (due to the additive effect) if the patient takes levodopa (Sinemet, Madopar), COMT inhibitors (Entacapone Stalevo), or dopamine agonists (rotigotine, pramipexole, ropinirole).

5.5. Side effects with levodopa

Mucuna should not be used in individuals with known allergy or hypersensitivity to *Mucuna pruriens* or components. There have been some side effects of *Mucuna*. In a study of patients with Parkinson's disease, a derivative of *Mucuna pruriens* caused minor adverse effects, which were mainly gastrointestinal in nature. Isolated cases of acute toxic psychosis have been reported [51] probably due to levodopa content. Therefore, as with Sinemet and Madopar, its use should be avoided in patients with psychosis or schizophrenia.

5.6. Specific warning about *Mucuna*

We assume that all contraindications, interactions, precautions, and side effects that we know about synthetic levodopa should be considered when taking levodopa from *Mucuna*.

Specific contraindications include thinning of the blood (anticoagulants), and care should be taken with antiplatelet and anti-inflammatory drugs because *Mucuna* increases clotting time. *Mucuna* should not merge with anticoagulants (Sintrom, Dabigatran, heparin, warfarin) or with antiplatelet drugs such as clopidogrel. Caution should be exercised, and the additive effect should be taken into account if it is associated with acetylsalicylic acid and nonsteroidal anti-inflammatory drugs (NSAIDs).

We should also be careful with antidiabetic medicines: *Mucuna* lowers glycemic index, and thus is to be considered a potential additive effect. Other interactions are possible, so always consult your regular doctor. On the one hand, it can be argued that *Mucuna* has been used for many centuries in India and has been available for several years online without a prescription, and yet serious problems have not been revealed. But that is just an observation.

Regarding Sinemet and Madopar, we have thousands of controlled studies, while publications on *Mucuna* are still scarce. One must therefore use greater caution when choosing *Mucuna*. While the future appears to be positive, we need the confirmation of more scientific studies.

6. Dosage and presentations

To use *Mucuna* correctly, the premise is to be clear about what you want: it is simply a legume that contains levodopa naturally. Synthetic levodopa usually used in pharmaceutical preparations may be replaced in whole or in part by the levodopa contained in *Mucuna*.

This sounds simple, but the point is that the dosages and concentrations can vary, so the guidelines must be individualized, and as we said, at present the patients (and even some doctors) lack sufficient information.

6.1. Before using *Mucuna*

It is essential to find a neurologist who is interested in *Mucuna* and who is adequately informed about this amazing plant and how it can influence the treatment of Parkinson's disease. You should confirm everything with him and not conceal any information that may affect the treatment of your disease.

6.2. A strategy to start using *Mucuna*

First of all, ask your neurologist who knows your case. He can tell you if you can be treated with *Mucuna* or not, based on your specific situation, based on the stage of your Parkinson's disease, and taking account other pathologies and conditions.

Secondly, your doctor will advise you on the purchase of the adequate formulation of *Mucuna* depending on the dose administered. It is prudent to start with low-dose tablets and subsequently increase gradually; there is always time to increase the dosage. Patience is key in the beginning: if you rush treatment for quick results, it is likely that you will experience some side effects which, although they are usually mild, can be bothersome. If the treatment proceeds too slowly on the other hand, you may think that the *Mucuna* is not working and give up.

Third, adjustment of the treatment: you almost always have to modify the dose and frequently have to remove some of the drugs previously prescribed (for Parkinson's disease or for your other pathologies).

6.3. Careful with mistakes in dosage

There is no proven effective dose for *Mucuna*. In clinical studies, some patients take 15 to 30 grams (half an ounce to one ounce) of *Mucuna* preparation orally for a week, but I discourage such quantities, which I consider too high.

Any medication (which *Mucuna* is) should be administered initially in small amounts, keeping in mind the particular case of the patient and the purpose of the treatment. Doses of 15 and 30 grams of *Mucuna* seed extract were used for a specific experiment, with strict medical checkups, knowing well the formulation of the product and its origin and taking into account many other factors.

The researchers work under controlled conditions: they select patients without contraindications and remove any incompatible drugs and other medications that may alter the absorption or metabolism of levodopa, etc. That is not what happens when a patient buys *Mucuna* just anywhere and self-medicates with little information and without medical supervision.

6.4. Be careful when buying *Mucuna*

A consumer may purchase capsules of 200 mg of levodopa with a 15% concentration or 800 mg tablets with a 50% concentration, and these are two completely different products. Sometimes patients have bought the product on eBay knowing nothing of their provider, and they receive a package whose content is not guaranteed and whose concentration is not safe. The patient then will then dilute the material in water without knowing how much to measure out. Always use *Mucuna* extracts that are dispensed by known, reliable suppliers. In the final chapter, we give a brief description of some of these.

6.5. Presentations

They are so widely available that the Internet is flooded with numerous commercial offers. In summary the presentations of *Mucuna* may be grouped into seven sections: (1) powder; (2) tinctures or concentrated extracts; (3) low-dose (15 to 30 mg of "real" natural levodopa) capsules or tablets, ideal to start taking *Mucuna*; (4) medium- or (5) high-dose capsules or tablets, (6) tincture or *Mucuna* drops, and (7) *Mucuna* mixed with other substances.

The classic presentation of *Mucuna*, the only one used in clinical trials, is powder from *Mucuna* seeds. It is very bothersome to prepare as the powder must be diluted in water or other liquid (not milk because it hinders absorption). It has a very unpleasant taste that laboratories try to hide by sweetening it. The great advantage is the ability to adjust the exact for smaller doses that are always recommended at the beginning. In countries (such as Spain) where it is more difficult to find capsules or tablets with small doses, one may start with *Mucuna* powder. There are many brands offered, but here I describe only the original, which is sent directly from India.

6.6. Zanpora HP-200

This drug was marketed in India after the publication of an innovative study in Parkinson's disease patients in which an average of six sachets (±3) of *Mucuna* seed powder (7.5 grams with levodopa 250 mg, i.e., 3.3%) were administered to each patient.

I would like to emphasize that this *Mucuna* levodopa dose is relatively high (1500 milligrams), especially for those who had never taken levodopa, and if combined with one or two tablets of Sinemet, there is an obvious risk of overdose. Other than those patients, there were no problems probably because this natural levodopa is not combined with carbidopa (as in Sinemet). In theory the levodopa from *Mucuna*, as it lacks carbidopa, should be removed rapidly from the blood, unless the plant contains other ingredients to avoid it.

After taking the *Mucuna* powder (dissolved in water), blood levels of levodopa behave similarly to those observed with the synthetic version of levodopa. The difference is that the maximum dose does not show as marked an effect [45] and clinical efficacy is similar or greater.

6.7. Common mistakes in prescribing Zandopa

Equivalences of Zandopa powder are administered to people who take only levodopa (without carbidopa), something which hardly occurs in the West, so that errors are very common.

According to the manufacturer, every measure of *Mucuna* powder (7.5 grams) is equivalent to 250 mg of synthetic levodopa. But this is only when the patient does not take carbidopa at all. However, almost all patients mix *Mucuna* powder with some Sinemet or Stalevo in which case it is necessary to assume that the carbidopa is working.

The equivalence for Zandopa is not clear to the uninitiated. If you follow the laboratory indications, you must give 30 grams of powder to replace the Sinemet 25/250 tablet (four small cups). This is the ratio that was used in the original study, but in practice it is too high and can cause side effects (nausea, vomiting, and malaise) so I do not recommend it. The dosage is individualized, and you have to start with small, adequately spaced doses. The laboratory has verified this and thus expressed it in the brochure, although not sufficiently emphasized.

7. *Mucuna* and conventional levodopa

Mucuna preparations usually sold online contain small amounts of levodopa. Furthermore, it is not combined with (carbidopa-like) "enhancers" and so has hardly any effect on symptoms.

As previously stated, in order to achieve the clinical effect of a tablet of Madopar or Sinemet, 1000 mg of levodopa *Mucuna* must be given. That would be like 4 scoops (30 g of seed powder) of Zandopa or nearly 17 capsules of other preparations providing 60 mg per dose. For example, a patient taking four daily tablets of Sinemet or Madopar who wants to switch to *Mucuna* alone would need 4000 mg natural levodopa daily, i.e., 120 mg of seed powder (a bottle of Zandopa contains 175 mg) or 66 capsules of Bonusan (60 mg levodopa each) or 40 capsules of Solbia (100 mg levodopa each). Few patients want to take on such a cost.

The problem is further complicated by the fact that the actual content of levodopa in many products sold online is lower than stated on the label [52].

7.1. Adding carbidopa to *Mucuna*

The synthetic levodopa in Sinemet is enhanced by carbidopa. This increases its clinical effectiveness and prevents peripheral side effects (nausea, tachycardia).

Carbidopa further improves the effects of *Mucuna*: it reduces the mild side effects and doubles or triples its effectiveness. This factor must be taken into account when a patient combines *Mucuna* and Sinemet (or Madopar or Stalevo): the carbidopa in these drugs also interacts with the natural levodopa in *Mucuna* by strengthening its clinical effects, and the dose should be greatly reduced.

And what happens when the patient does not take Sinemet or other drugs? Then *Mucuna* may be insufficient. These patients complain that *Mucuna* "does not do anything," and this is due to the fact that their decarboxylase is quickly removed from the blood, without allowing time for a sufficient amount to reach the brain.

The solution seems to be to add carbidopa, which in some countries is sold separately (as Lodosyn). When Lodosyn is not available, there is the option of taking half a tablet of Sinemet Plus (12.5 mg carbidopa) and subtract the amount of synthetic levodopa (50 mg), taking into account that it will now be more potent.

7.2. Enhancing levodopa

One inexpensive and clinically effective option is to use levodopa enhancers that are contained in conventional drugs. It is a good idea to mix the *Mucuna* seed powder with very low doses of Madopar (e.g., half a tablet in the morning and half at night). Thus, only 200 mg of synthetic levodopa is provided, but this has the advantage that there are 50 mg of benserazide included. This will greatly enhance the effectiveness of natural levodopa in the added *Mucuna*.

One can also add green tea; its polyphenols are inhibitors of decarboxylase (such as benserazide or carbidopa), further reinforcing the levodopa. The overall bioavailability of levodopa will be improved. In some patients a spectacular result has been obtained, as we have previously published [53, 54].

7.3. Risks of combining *Mucuna* and green tea

Green tea enhances the effect of beans in general and of *Mucuna* in particular. This effect can also be seen in patients taking Sinemet or Madopar: it is recommended that patients be aware of this phenomenon due to the increase in potency it can produce.

Carbidopa-like effect. There is something in green tea that acts like carbidopa. It contains polyphenols which inhibit dopa-decarboxylase [55], an action similar to that carried out by the carbidopa or benserazide contained in Sinemet or Madopar.

Entacapone-like effect. In addition, there is something that acts like entacapone in green tea. Polyphenol, epigallocatechin gallate (EGCG) promotes the entry into the brain of levodopa and prolongs its bioavailability in the bloodstream because it inhibits the COMT enzyme [56]. This action is similar to that of entacapone, namely, that beans mixed with green tea have Stalevo-like effects but with different proportions. Obviously, if you take levodopa (*Mucuna*

or otherwise), its effectiveness will be reinforced, and this should be taken into account as there is risk of overdose. Always consult your doctor.

These "carbidopa-like" and "entacapone-like" effects can be seen with green tea, and they are independent of their other neuroprotective benefits [57] so the tea is recommended for many Parkinson's disease patients.

7.4. Complexities of adjusting *Mucuna*

As *Mucuna* seed powder does not contain carbidopa (theoretically), the clinical effectiveness of 1000 mg of natural is equivalent to a tablet of Sinemet 250/25 or of Madopar 200/50 (**Figure 1**).

7.5. *Mucuna*: the levodopa for the poor

In Africa and the Caribbean, I have seen Parkinson's disease patients in a very deteriorated state, who are not treated with levodopa because they are unable to afford Sinemet, Madopar, or Stalevo. Neither they nor their governments can bear this expense. Ironically in their countries, levodopa is everywhere; *Mucuna* grows spontaneously and spreads so fast that they even have to pull up it so it does not invade other crops.

The plant contains a large amount of levodopa, a treasure trove for those patients in the third world. Ailing inhabitants need this levodopa to live better and longer. It is outrageously unfair. A recent study [58] offered an option: the use of *Mucuna* levodopa is very accessible in countries that cannot afford Sinemet, Madopar, or Stalevo.

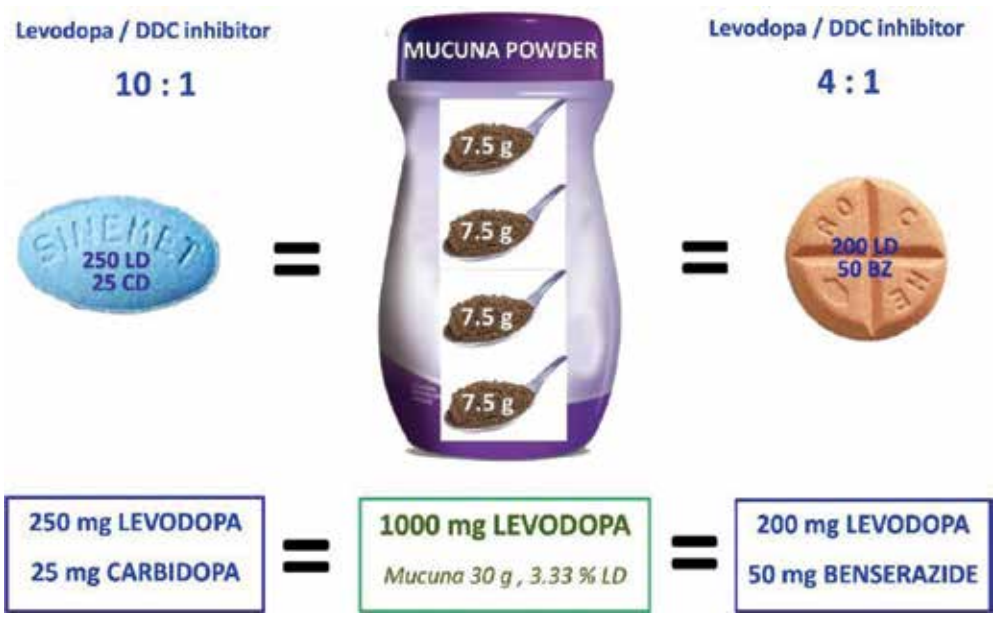

Figure 1. Clinical effectiveness of *Mucuna* compared with Sinemet and Madopar [54] (see text).

7.6. Neurologists in Ghana and Zambia

I applaud the laudable deeds of neurologists who have opened clinics for patients in Ghana and Zambia where they have already served over 100 patients. There they cannot prescribe Sinemet because it costs a prohibitive dollar and a half each day per patient; meanwhile *Mucuna pruriens* grows spontaneously all around them. With the collaboration of the local authorities, they began to systematically prepare seeds of *Mucuna* (harvesting 12 different types) cooking them first to eliminate antinutritive substances.

They administered *Mucuna* without special extraction methods, although they could not integrate carbidopa, and have obtained the first results: the levels of levodopa in the blood increase, demonstrating that it is being absorbed [58, 59]. Patients improved although the system is so primitive that they suffered some side effects such as nausea, dry mouth, and orthostatic hypotension [59].

The initiative of these pioneers of *Mucuna* treatment in Africa is promising. However, this situation must be regulated. Who could ever infringe on such an important humanitarian effort?

Studies of *Mucuna* in Parkinson's disease should be expanded. Inexpensive levodopa should be provided to patients with few resources in poor countries. It could be that doctors and patients of the West finally imitate the less fortunate.

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Edited by Sarat Chandra Yenisetti

Parkinson's disease (PD) is the second most common neurodegenerative disorder results due to loss of dopamine producing brain cells. Knowledge relating to PD condition has been known since 5000BC, however no effective therapeutic strategies are available till today. Therefore it is important for neurobiologists to work further by taking advantage of modern scientific methods and develop appropriate therapeutic strategies. Efforts in this direction are worthy as they will reduce the burden of PD among elderly, who are already burdened with age related systemic degenerative processes. This book is a humble effort in that progressive direction. It has chapters covering multiple aspects relating to etiology, pathophysiology of PD, available and futuristic therapeutics strategies. Therefore it will be of interest to common man, biomedical researchers and clinicians. This is one small step in a direction "to reduce the burden of neurological disease."

Published in London, UK

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ISBN 978-1-83881-459-5