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Non-Motor Symptoms in Parkinson's Disease Patients—An Observational Study

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Abstract

Background: Parkinson's disease (PD) remains a challenge for neurologists, particularly in its advanced stages when non-motor symptoms become a burden for the patient. While motor symptoms may be satisfactorily controlled with levodopa therapy or continuous levodopa/carbidopa intestinal gel (LCIG) administration, autonomic, sleep and mental disorders are hard to treat. During the last years, researchers have shifted their interest more to non-motor symptoms, PD being now considered a complex multiorgan impairment. **Objective:** The aim of this study was to describe non-motor symptoms in 40 Romanian patients diagnosed with PD, under conventional and LCIG administration treatment. **Methods:** A cross-sectional observational study was conducted, consisting of two groups of 20 patients each: the first group comprised PD patients who received conventional Levodopa treatment, while the second group was formed of patients receiving LCIG therapy. Various data concerning patient's age, gender, duration of illness, comorbidities, motor and non-motor symptoms were recorded. The data were processed in SPSS v.20. **Results:** Subjects under continuous LCIG administration, although showing amelioration of motor symptoms, complained more frequently of constipation, mental, and sleeping disorders (statistically significant). Regarding anosmia, orthostatic hypotension, hypersalivation, urinary incontinence and restless legs syndrome, no statistical significant difference was observed between the two groups ($p > 0.05$). **Conclusion:** Nowadays, more research is conducted on non-motor symptoms in PD patients, as therapeutic measures try to limit these burdens, in order to improve patient's quality of life.

Keywords

Parkinson's Disease, Non-Motor Symptoms, Conventional Treatment, Levodopa/Carbidopa Intestinal Gel

1. Introduction

Parkinson's disease (PD) is a complex neurodegenerative neurological disease resulting from the destruction of dopaminergic neurons from the substantia nigra pars compacta. This lack of dopamine will determine the apparition of a complex of both motor and non-motor symptoms, with an average age of onset at 60 years, with a clear increase in incidence with advanced age [1].

Although PD is defined by the progressive loss of dopaminergic neurons, other neurotransmission systems (noradrenergic, cholinergic, and serotoninergic) degenerate concomitantly [2]. These non-dopaminergic lesions reflect the disease's clinical heterogeneity, with symptoms and non-resistance to conventional therapy varying between patients [3] [4] [5].

Clinically, early PD is dominated by motor symptoms, including bradykinesia, rigidity, resting tremor, and postural instability, as the initial complaints that bring the patient to the neurologist, as well as the main diagnostic criteria (UKPDSBB Criteria) [4]. Because motor characteristics in patients are heterogeneous, specialists have attempted to classify the condition into subtypes [6] [7]. Consensus regarding these subtypes remains elusive, but empirical clinical observations suggest two major subtypes: PD with dominant tremor (with relative absence of other motor symptoms) and PD without dominant tremor (which includes phenotypes described as akinetic syndrome and stiffness and walking disorders with postural instability) [8] [9]. An additional subgroup of patients has a mixed or indeterminate phenotype with multiple motor symptoms of varied severity [10]. The evolution and prognosis of the disease differ between the subtypes; PD with dominant tremor is often associated with slower progression and lower functional disability [10] [11] [12].

However, the concept of PD strictly as a movement disorder is considered outdated because non-motor symptoms influence the patient's diagnosis, prognosis, and quality of life (QoL) considerably [13] [14]. Thus, numerous researchers focused during the last years on the detection and treatment of non-motor symptoms in patients with PD. Some authors suggested that pain, hyposmia, apathy, anxiety, mood disorders, or subtle cognitive dysfunction may emerge first and are often overlooked by the patient or incorrectly diagnosed [15] [16] [17]. Additionally, cardiovascular dysautonomia (orthostatic hypotension, rhythm disorders), gastrointestinal impairments (dysphagia, delayed gastric emptying, constipation), genito-urinary impairments (urinary incontinence, sexual dysfunction), thermoregulation dysfunctions, and sleep disorders may occur; the pathophysiology of these complains still need to be determined [18] [19] [20].

Neuropsychiatric disorders, one of the most common non-motor symptoms, are exacerbated by cognitive impairments, such as memory loss, confusion, and hallucinations [18]. Timmer and colleagues showed that, among such neuropsychiatric conditions, the major predictor of poor QoL remains the severity of depression and cognitive dysfunction [21] [22].

According to Goodarzi *et al.*, depression is another non-motor symptom commonly encountered in PD patients, being characterized by apathy, fatigue, irritability, indecision, and sadness, although these symptoms may also occur in subjects with PD who are not depressive [23]. Numerous factors complicate the diagnosis of depression in patients with PD, such as the absence of typical depression symptoms (shame, guilt, sadness), while sex may also play a role, as stated by Perrin *et al.* [24].

Some studies were also conducted on the autonomic disturbances in PD [25]-[30]. While α-synuclein pathology is the main cause behind Lewy body formation in the nigrostriatal pathways underlying the classic PD symptoms, the peripheral autonomic nervous system is also vulnerable to such changes [25]. The pathophysiology of autonomic dysfunction in PD is thought to result from dysfunctions of some mediating nuclei of autonomic functions, such as the vagal nucleus, the ambiguous nucleus, and other medullary centers [26] [27]. This deterioration is associated with an impaired vegetative nervous system, including sympathetic ganglionic disorders, the mesenteric plexus of the gastrointestinal tract, and sympathetic cardiac afferents [28] [29] [30].

Urinary incontinence in persons with PD may result from a spastic bladder, whereby the bladder becomes hyperactive and contracts uncontrollably, according to Merola *et al.* [30]. However, spastic bladder is not the most common cause of urinary incontinence in PD: recent studies have suggested various causes, including abnormal processing of sensory signals from the bladder as well as adverse effects of PD treatment [31].

An interesting topic for researchers is sexual dysfunctions, as these may significantly deteriorate the QoL for PD patients and their partners [32]. Men experience erectile dysfunction and ejaculatory problems, while women experience lubrication loss and involuntary urination. Loss of desire, avoidance, and anxiety are common to both sexes [32] [33].

Syncope caused by postural hypotension is another common manifestation of vegetative dysfunction [34] [35]. Lesions of the autonomic nervous system affect the physiological mechanism that compensates for hypoperfusion of the brain by increasing heart rate and vascular constriction to increase blood pressure. Persistent use of dopaminergic agonists can lead to postural hypotension [36]. Orthostatic hypotension can cause PD patients to fall, which can lead to severe disability [37].

Gastrointestinal dysfunctions are also prevalent in PD patients, constipation, dysphagia, malnutrition, and hypersalivation being the most frequent complains according to several studies [38] [39]. Damage to the dorsal nucleus of the vagus nerve causes impaired gastrointestinal function along with disruption of the enteric nervous system, as α-synuclein accumulation in the enteric nervous system and the vegetative ganglion may be the main cause [39].

Several therapeutic approaches are currently deployed to ameliorate motor and non-motor symptoms, both initially and in the advanced stages. Compensation for dopamine deficiency in the striatum secondary to the loss of dopaminergic

neurons in the substantia nigra has been attempted via oral intake of levodopa plus dopa-decarboxylase inhibitor [40]. Numerous drugs designed to regulate motor fluctuations are available, including dopamine agonists and non-dopaminergic agents, such as amantadine, monoamine oxidase-type B (MAO-B) inhibitors, and catecol-O-methyl-transferase (COMT) inhibitors [41] [42] [43].

Despite numerous scientific advances, the disease remains progressive, and medication becomes less effective over time. Prolonged treatment with oral levodopa is associated with both motor and non-motor complications because, physiologically, the striatal dopaminergic receptors receive dopamine continuously, while oral treatment implements a pulsatile administration rate [44]. End-of-dose wearing-off phenomena, including dyskinesia, early morning akinesia, and unpredictable motor fluctuations, require careful adjustment of levodopa dosage until the optimal balance is identified [40]. In advanced stages, for subjects with severe motor complications, continuous infusion of medication is desirable and may be realized by several modalities, including continuous subcutaneous apomorphine infusion, continuous levodopa delivery by intestinal infusion (continuous LCIG infusion through Duodopa® pump), transdermal levodopa application, micro-encapsulated levodopa application, or pallidal or subthalamic nucleus deep brain stimulation (DBS) [45] [46].

In Romania, patients with advanced PD may supplement oral replacement therapy with specially implanted portable pumps that continuously administer Duodopa® gel (levodopa 20 mg/ml + carbidopa monohydrate 5 mg/ml intestinal gel) directly into the duodenum or the upper portion of the jejunum through a permanent tube mounted by percutaneous endoscopic gastrostomy (PEG). The indications for pump installation focus primarily on motor symptoms (long and frequent "off" periods) that are insufficiently managed by optimized oral medication [47]. The process of switching from intermittent oral medication to continuous infusion is laborious, since the installation of the device requires multidisciplinary collaboration between a gastroenterologist, radiologist, and general surgeon [48]. Optimal operation of the device requires sensitizing the patient and their relatives, and close connection with caregivers is desirable for rigorous and frequent monitoring and in case of adjustment to the morning dose, the continuous rate, or the extra dosage rate, but also in case of local and general complications [49].

Several contraindications have been identified regarding the initiation of this therapy, including hypersensitivity to levodopa, carbidopa, or any of the excipients; severe liver and renal insufficiency; severe heart failure; severe cardiac arrhythmia; acute stroke; narrow-angle glaucoma; and endocrine diseases, such as pheochromocytoma, hyperthyroidism, or Cushing's syndrome [50]. Concomitant administration of other drugs in PD should be executed with great care. Thus, non-selective MAO-B inhibitors and selective MAO-A inhibitors should be withdrawn at least two weeks prior to initiation of LCIG treatment and are not recommended for administration concomitantly with continuous Duodopa® infusion. Severe dementia may be a contraindication, as the patient may expe-

rience difficulties operating the device, but adequate family support improves the feasibility of this therapy [51] [52].

The patient and their relatives must be informed both in writing and orally prior to implantation, as progression to this type of treatment requires consent to several rules to ensure optimal functioning without adverse events or complications [53] [54]. Therapy expectations should be discussed prior to treatment so that the patient does not have unrealistic expectations. Safety measures are essential to the implementation of this device, and several studies attest that the Duodopa® pump is safe to use [50] [55] [56].

The aim of this study is to highlight non-motor symptoms in a cohort of 40 Romanian patients with advanced PD under both conventional levodopa oral therapy and continuous LCIG (Duodopa®) administration.

2. Materials and Methods

To conduct this cross-sectional observational study, we followed patients diagnosed with PD who were admitted between January 2017 and January 2019 to the hospital's neurology department and divided them into two groups of 20 patients each according to treatment type: the first group of patients was orally treated with levodopa, while subjects from the second group received continuous infusion of levodopa 20 mg/ml + carbidopa monohydrate 5 mg/ml intestinal gel.

The following inclusion criteria were applied: all patients had been diagnosed with PD (disease duration of at least six months) according to the United Kingdom Parkinson's Disease Society Brain Bank (UKPDSBB) Clinical Diagnostic Criteria. All patients were aged at least 18 years and participated voluntarily in this study. Patients with severe speech disorders or major cognitive disorders, those who refused to participate, and those without complete medical data were excluded.

The patients were clinically and paraclinically examined as part of the follow-up strategy. Past medical data were accessed via patient medical files. The PD was staged based on the Hoehn-Yahr (HY) scale, which records the severity of motor symptoms from stage I to IV.

Continuous variables were presented as mean ± standard deviation and compared using the Student's T-test; categorical variables were expressed as numbers and/or percentages and compared using Pearson's chi-squared test. All statistical tests were two-tailed, with p-value < 0.05 considered statistically significant, and performed in IBM's SPSS Statistics version 20.

3. Results

The study's results were divided into three parts: first, a descriptive analysis of the demographic data (gender, age, duration of illness) of both patient groups was performed; next, the differences in associated comorbidities were highlighted; finally, the effect of continuous LCIG administration on non-motor symptoms was revealed.

Demographic data

Both patient groups predominantly included male patients, but this demographic parameter was not statistically significant in the present study. Patients' mean age during the study was higher in the group receiving Duodopa® pump therapy (63.55 ± 9.85 years vs. 66.45 ± 5.46 years). Statistical analysis did not reveal this parameter to be statistically significant (p = 0.322). The mean age at which the positive diagnosis had been established was equal in both groups. The time interval from disease onset and inclusion in the study was significantly higher among patients receiving continuous LCIG administration (8.30 ± 4.53 years vs. 11.30 ± 3.71 years), and this parameter was statistically significant (p = 0.028) (Table 1). Regarding the distribution of patients according to Modified HY staging, 40% of them were at stage IV, while 30% were at stages II and III, respectively.

Associated comorbidities

The presence of comorbidities is a statistically significant parameter for patients under conventional treatment (p = 0.007). In the first group, 20% of patients and 25% in the second group were diabetic, a parameter with statistical impact in the present study (p = 0.001). Hypertension was observed in a higher percentage of patients in the first group, its presence proving significant in the statistical analysis (p = 0.027). Osteoporosis was observed in both groups, more prevalently among those treated with the pump (25% vs. 40%), with the statistical analysis showing a p-value of 0.027. Experience of depression prior to inclusion in the study in patients of the first group (p = 0.025) is also included as a parameter with statistical impact. Forty percent of patients in the second group had chronic ischemic heart disease. Anemia is also within the statistically significant (p = 0.025) parameters and was observed in 25% of patients in the second group. Camptocormia was observed in 50% of patients receiving continuous LCIG administration (Table 2).

Non-motor symptoms

Numerous non-motor symptoms were analyzed in both groups (Table 3). Constipation, sleeping disorders, and mental disorders were more frequent in subjects receiving continuous LCIG administration (statistically significant). Although orthostatic hypotension, restless legs syndrome, and hypersalivation were less likely in patients receiving Duodopa® pump therapy, no statistical significance was observed. Anosmia and urinary incontinence remain unresolved despite antiparkinsonian therapy.

4. Discussion

PD, particularly in its advanced stages, remains a major neurological neurodegenerative pathology that impacts the patient's life considerably. While motor symptoms were previously prioritized for treatment, increasing emphasis is now given to non-motor symptoms. Non-motor characteristics precede motor symptoms by several years, with anosmia and constipation present from the beginning. Comparing non-motor with motor manifestations, we observed that non-motor

symptoms are present from the beginning and are found with individual variations at all stages of the disease. Moreover, with aging and as the disease progresses, non-motor components continue to develop, further impacting the patient's QoL.

Table 1. Demographic data for both patient groups.

Parameter	Conventional therapy (n = 20)		Levodopa/carbidopa intestinal gel continuous administration (n = 20)		p-value
Sex	Female	8 (40%)	Female	5 (25%)	0.311
	Male	12 (60%)	Male	15 (75%)	
Age	63.55 ± 9.85		66.45 ± 5.46		0.322
Age at diagnosis	55.25 ± 6.76		55.05 ± 5.45		0.978
Disease duration	8.30 ± 4.53		11.30 ± 3.71		0.028
Modified Hoehn & Yahr Scale	**Conventional therapy (n = 20)**				**p-value**
2	6 (30%)				
3	6 (30%)				0.819
4	8 (40%)				

Table 2. Comorbidities in patients with PD.

Parameter	Conventional therapy (n = 20)	Levodopa/carbidopa intestinal gel continuous administration (n = 20)	p-value
Comorbidities	4 (20%)	-	0.007
Diabetes	4 (20%)	5 (25%)	0.001
Hypertension	7 (35%)	6 (30%)	0.027
Osteoporosis	5 (25%)	8 (40%)	0.027
Previous depression	5 (25%)	-	0.025
Ischemic cardiomyopathy	-	8 (40%)	0.371
Anemia	-	5 (25%)	0.025
Camptocormia	-	10 (50%)	1

Table 3. Non-motor symptoms in PD patients.

Parameter	Conventional therapy (n = 20)	Levodopa/carbidopa intestinal gel continuous administration (n = 20)	p-value
Anosmia	11 (55%)	12 (60%)	0.343
Constipation	13 (65%)	14 (70%)	0.027
Orthostatic hypotension	12 (60%)	9 (45%)	0.752
Restless legs syndrome	12 (60%)	10 (50%)	0.527
Sleeping disorders	11 (55%)	16 (80%)	0.027
Hypersalivation	11 (55%)	7 (35%)	0.527
Mental disorders	12 (60%)	16 (80%)	0.011
Urinary incontinence	7 (35%)	14 (70%)	0.752

In both patient groups in this study and in previous studies, almost all systems were affected. Numerous manifestations were found, rendering the development of new therapies imperative. Intermittent oral therapy with levodopa will eventually become insufficient to meet the patient's needs. Motor complications emerge, including the wearing-off phenomenon toward the end of the dose, freezing in the "off" stage, and dyskinesia in the "on" stage, all of which exacerbate the patient's weakening state. Based on international guidelines, we are considering switching to continuous infusion treatment with Duodopa® when a patient with advanced PD develops severe motor fluctuations and hyper-/dyskinesia and the valid and recommended oral medication fails to yield satisfactory results. Indications for installing a Duodopa® pump are long and frequent "off" periods and when other methods of continuous dopamine substitution, such as DBS or apomorphine pump, are contraindicated, inefficient, or unavailable [57].

Improvement of motor symptomatology and of the patient's QoL under Duodopa® treatment is well attested [58] [59]. However, in Romania, the benefits of the Duodopa® pump for non-motor manifestations remain underexplored [60].

Globally, most studies have focused on the effects of LCIG on motor symptoms. The results unequivocally indicate that this therapeutic strategy offers improvements, including reduced "off" periods, increased "on" periods without debilitating dyskinesia, and reduction of troublesome dyskinesia [47] [50].

We found that PD is more predominant in male patients, but we cannot conclude that gender significantly influences the severity of PD's clinical presentation, as noted by Picillo *et al.* [61].

Patients undergoing continuous LCIG administration were older and had longer disease durations than subjects receiving conventional therapy, which may be explained by the fact that the Duodopa® pump is a second-line therapy suitable for advanced PD and patients living for many years with PD diagnosis.

Evaluated patients presented numerous comorbidities, including diabetes, hypertension, previous depression, osteoporosis, anemia, and camptocormia. The relationship between diabetes and PD remains controversial, although in this study we found statistical significance between the two pathologies, regardless of treatment type. Hypertension was associated with oral levodopa therapy, and personal variations were the only explanation for this correlation. Osteoporosis, camptocormia, and anemia are associated with elderly patients with long duration of the disease, as characteristics of advanced PD treated with LCIG.

Other studies have also focused on LCIG's influence on non-motor manifestations in patients with PD at different stages, confirming their improvement and enhanced QoL. However, they mentioned only a few of the symptoms, including drowsiness, fatigue, and cardiovascular and urinary function [61] [62] [63] [64] [65]. This study's findings confirm the trends observed in other countries, including the Greenfield observational study conducted by Lopiano *et al.* (2019), in which patients with LCIG infusion showed significant improvements in motor fluctuations, ADL, and QoL that are similar to those in this study's population. Other studies have shown that, in patients with advanced PD, early and

regularly monitored treatment with LCIG improves motor and non-motor symptoms and ADL. For example, a study by Fasano *et al.*, 2012 that included a few patients undergoing LCIG treatment reported this treatment's efficacy for non-motor symptoms [66].

Regarding the effects of medication on sleep disorders, our study showed that continuous LCIG administration may potentiate insomnia and fatigue as adverse effects of dopamine. However, this contradicts findings from earlier studies, whereby sleep disorders seem to improve under continuous levodopa administration. We found two studies in which the team of neurologists, with the help of polysomnography after six months of therapy, verified these improvements with exact measurements [67] [68].

Constipation is a major complication of LCIG treatment, as revealed in other studies [69]. Mental disorders are a burden for the PD patient and affect predominantly patients under Duodopa® pump treatment. This may be an effect of long-term dopamine administration.

Orthostatic hypotension seems to affect more patients undergoing conventional therapy than subjects with Duodopa® pumps, but no statistical significance was found, in line with other studies [70] [71] [72] [73] [74].

Hypersalivation was also diminished in patients undergoing continuous LCIG administration, though without any statistical significance. No objective method was used to measure the quantity of saliva in our patients, although this was recommended in other studies [75].

Urinary incontinence is a common problem in older people, regardless of the presence of PD. We assessed the extent of this symptom in both groups of patients, without statistically significant differences. A study by Rana *et al.*, 2015 corroborates our results [16]. Moreover, urinary incontinence is found twice as often in PD patients than in healthy elderly patients.

5. Limitations and Strengths

The study's main limitation is the small number of participants. However, it was not a multicenter study. Moreover, in Romania, treatment with the Duodopa® pump is still nascent, with few patients receiving this therapy at national level.

Another limitation was the lack of correlation between patients' QoL and treatment type in this Romanian cohort, a topic studied by numerous international authors [76] [77] [78] [79] [80]. However, further research on this cohort with respect to other important aspects of the Duodopa® pump treatment is planned.

6. Conclusions

PD manifests with motor symptoms as the main diagnostic criteria and treatment target. However, progressive non-motor symptoms are also present, affecting multiple systems. Administration of oral substitution treatment improves motor symptoms concomitantly with a degradation of non-motor manifestations.

Thus, advanced PD requires another therapeutic approach, and continuous administration of LCIG is currently the preferred solution in Romania.

This study found that constipation, sleeping disorders, and psychiatric disorders are the most common non-motor symptoms encountered in patients receiving continuous LCIG administration, with other non-motor characteristics influencing patients' QoL, corroborating other studies from different centers [81] [82] [83] [84].

The study represents a necessary contribution, particularly in Romania, where the treatment of advanced PD remains in development and any data regarding the patients' experiences of continuous LCIG treatment are interest. Moreover, this study sensitizes the complexity of PD, which is not merely a movement disorder, but a disease with multi-systemic impairment, in which the patient's QoL will be significantly enhanced by the improvement of non-motor symptoms.

Ethics Approval and Consent to Participate

This study was approved by the institutional ethical committee and the chief doctor of the neurology clinic, and informed consent was obtained from all patients. The study was conducted in accordance with the principles of the International Conference on Harmonization Good Clinical Practices.

Human and Animal Rights

All clinical investigations were conducted according to the principles of the Declaration of Helsinki, and no human rights were violated.

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Conflicts of Interest

The author states that there was no conflict of interest. All costs regarding study design, research, data collection, analysis, writing, reviewing, and approving the publication were borne by the author.

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