

Motor and Non-Motor Symptoms in Parkinson's Disease: Effects on Quality of Life

Elif GÖKÇAL, Veysel Eren GÜR, Rabia SELVİTOP, Gülsen BABACAN YILDIZ, Talip ASİL

Department of Neurology, Bezmialem Vakıf University School of Medicine, İstanbul, Turkey

ABSTRACT

Introduction: This study aimed to evaluate motor and non-motor symptoms in idiopathic Parkinson's disease (IPD) patients and to determine the self-reported influence of all existing symptoms on their quality of life (QoL).

Methods: The sociodemographic and clinical characteristics, medical treatments, and Modified Hoehn and Yahr (mH&Y) scores of IPD patients without cognitive impairment were recorded. A survey questioning different motor and non-motor symptoms was administered to the patients. The patients were asked to rate their symptoms by number from the greatest influence to the least influence on their QoL. Subjects were divided into two groups: those suffering from IPD for ≤5 years (Group 1) and those suffering from IPD for >5 years (Group 2). These groups were compared in terms of sociodemographic and clinical characteristics, existing symptoms, and influences of these symptoms on their QoL.

Results: There were 63 patients in Group 1 and 37 patients in Group 2. No statistically significant differences were detected between the groups with respect to sociodemographic characteristics or mH&Y scores. The most common motor symptoms in both of these groups

were tremor and bradykinesia; meanwhile, the non-motor symptoms most frequently encountered in these groups were pain-cramps, constipation, and excessive daytime sleepiness (EDS). Again, while the symptoms that most greatly disturbed QoL in all patients were reported to be tremor and bradykinesia, the most disturbing non-motor symptom was frequent voiding/incontinence, which was a less common symptom. Pain-cramp, constipation, and EDS, which were the most frequent non-motor symptoms, were the symptoms that least disturbed QoL.

Conclusion: It is widely accepted that motor symptoms determine QoL in IPD. However, non-motor symptoms are seen during all phases of the disease. The impact of non-motor symptoms on the QoL of IPD patients remains substantial. Therefore, in addition to the well-known motor symptoms, non-motor symptoms, which may be overlooked during physical examination yet may profoundly impact QoL, should be questioned and treated appropriately to improve QoL in PD patients as much as possible.

Keywords: Parkinson's disease, motor symptoms, non-motor symptoms, quality of life

INTRODUCTION

Idiopathic Parkinson's disease (IPD) is the most common neurodegenerative disorder after Alzheimer's disease (1). The major motor symptoms of IPD are resting tremor, bradykinesia, rigidity, and postural reflex disturbance. Apart from these dopaminergic motor symptoms, non-motor symptoms also develop secondary to serotonergic, noradrenergic, cholinergic, and autonomic nervous system involvement (2), including major neuropsychiatric symptoms, autonomous disorders, sleep disorders, and sensory symptoms (3). Non-motor symptoms are seen in about 90% of IPD patients in all stages of the disease (4). However, these symptoms are usually not recognized and are underestimated when planning therapeutic strategies (5).

Increased life expectancy owing to the emergence of new treatment options in IPD addresses the importance of quality of life (QoL) in the follow-up of IPD patients. Understanding the factors that most influence QoL is of paramount importance for treatment modalities that aim to optimize the functional and emotional status of patients.

The standard in QoL assessment is to achieve the best QoL for the individual, which itself is not only based on the healthcare provider's opinion but also relies on the subjective reports of affected individuals (6). Although QoL was earlier regarded as equivalent to functional status (7), current literature shows that in addition to functional abilities, QoL includes symptoms, treatment-related side effects, and social, psychological, mental, familial, and financial aspects (8).



Correspondence Address: Elif Gökçal, Bezmialem Üniversitesi Tıp Fakültesi, Nöroloji Anabilim Dalı, İstanbul, Türkiye
E-mail: elifdr99@gmail.com

Received: 29.12.2015 **Accepted:** 18.02.2016 **Available Online Date:** 11.11.2016

©Copyright 2017 by Turkish Association of Neuropsychiatry - Available online at www.noropskiyatrisivi.com

In this study, we aimed to evaluate motor and non-motor symptoms in IPD patients and to determine the self-reported influence of the extent of existing symptoms on their QoL.

METHODS

This study included IPD patients who received regular antiparkinsonian therapy and were followed in the Motor Disorders Outpatient Clinic of the Neurology Department of the Bezmialem Vakıf University School of Medicine between April 13 and July 02, 2015. Diagnosis of IPD was verified according to the UK Parkinson's Disease Brain Bank Clinical Diagnostic Criteria (9). In a face-to-face interview setting, the patient's age, gender, marital status, level of education, known comorbidities, IPD duration, first affected side of the body, current antiparkinsonian drugs, and clinical findings were recorded. Cranial magnetic resonance images (CMRI) were assessed in all patients. In addition, Mini Mental Status Examination (MMSE), Geriatric Depression Scale Short Form (GDS), and Modified Hoehn and Yahr Scale (mH&Y) scores were acquired for all patients.

After these screening assessments, patients with vascular parkinsonism, Parkinson-plus syndromes, history of diabetes or rheumatoid arthritis, or cognitive disorders based on clinical or MMSE scores were excluded from the study; patients with mH&Y scores <1.5 or >3 were also excluded.

This study was approved by the Bezmialem Vakıf University School of Medicine Ethics Committee of our hospital; the study subjects gave verbal consent after being informed about the purpose and method of the study.

A survey questioning the motor and non-motor symptoms seen in IPD was administered to 100 IPD patients. All questions were read to the subjects, and the details of their existing symptoms were collected. Afterwards, patients were asked to rate their symptoms by number, from the greatest influence to the least influence on their QoL. Each rating was read to the patient again and confirmed by the patient, and any amendments were made before confirmation. Non-referring explanations were given to patients who had difficulty understanding symptoms. The patients were also asked if any disturbing symptoms other than those questioned in the survey were present; these answers were recorded.

The subjects were divided into two groups: patients suffering from IPD for ≤5 years (Group 1) and patients suffering from IPD for >5 years (Group 2). These groups were compared in terms of sociodemographic and clinical characteristics, existing symptoms, and influences of these symptoms on their QoL.

Statistical Analysis

Statistical Package for the Social Sciences software for Windows, Version 22 (IBM SPSS Statistics; Armonk, NY, USA) was used for the statistical analyses. Mean, minimum, maximum, and percentage values were calculated for descriptive data. The chi-square test was used to compare categorical variables. After the normality of the data was determined by the Kolmogorov-Smirnov method, non-normally distributed data was compared by Mann-Whitney U test. Statistical significance was set at a p value of <0.05.

RESULTS

The mean age of the patients (n=100) was 65.22±10.7 (range: 34-85), consisting of 65 male and 35 female patients. The mean duration of the disease was 4.37±4, ranging from 1 to 22 years. The average mH&Y score was 2.12±0.5. GDS scores varied between 0 and 13, with a mean score of 4.09±2.8. The onset symptom was tremor in 72 patients, slow movement in 19 patients, mixed complaints in 8 patients, and spasm in one patient. Twenty-one patients were receiving levodopa, 15 patients were using dopamine agonists, and the remaining 64 patients were receiving combination therapy.

When classifying the subjects per disease duration, the rates of use of dopamine agonists alone, use of levodopa alone, and use of combination therapy in Group 1 (≤5 years, n=63) were 76.2%, 79.4%, and 61.9%, respectively, compared to 78.4%, 89.2%, and 67.6% in Group 2 (>5 years, n=37). These groups did not significantly differ in terms of medication use.

Also, no statistically significant difference was detected between the two groups with respect to sociodemographic characteristics, GDS, or mH&Y score (Table 1).

Among all surveyed questions, the 20 most frequently reported symptoms were assessed. The presence of these symptoms varied from 2 to 18 with a mean of 9.4±3 in all patients. The means were 9±3 (range: 1-18) and 10±2 (range: 5-17) in Group 1 and Group 2, respectively; these values were not statistically different. While the most common motor symptoms in both groups were tremor and bradykinesia, the non-motor symptoms most frequently encountered in these groups were pain-cramps, constipation, and excessive daytime sleepiness (EDS). Dyskinesia, falling, and fatigue were found to be significantly more frequent in group 2 (p=0.004, p=0.02, and p=0.02, respectively). Despite being non-significant, depressive symptoms (50.8%), anosmia (44.4%), decreased libido/sexual functions (39.7%), recognition of tremor by others (39.7%), and micrographia (25.4%) were more common in Group 1; meanwhile, bradykinesia (89.2%), pain-cramp (70.3%), slow gait (70.3%), EDS (64.9%), constipation (56.8%), REM sleep be-

Table 1. Sociodemographic characteristics and clinical scores between groups

| | Group 1 (time ≤5 years) | Group 2 (time >5 years) | p |
|--|--|---|----------|
| Number of patients | 63 | 37 | |
| Age, Mean±SD | 64.9±10.4 | 65.6±11.2 | 0.88 |
| Sex | | | |
| Female, n, % | 23, 36.5 | 12, 32.4 | |
| Male, n, % | 40, 63.5 | 25, 67.6 | 0.68 |
| Educational status | | | |
| Uneducated n, % | 10, 5.9 | 3, 8.1 | |
| At least elementary school n, % | 53, 84.1 | 34, 91.9 | 0.26 |
| GDS, Mean±SD | 4±2.9 | 4.2±2.8 | 0.58 |
| mH&Y Score, Mean±SD | 2.07±0.5 | 2.21±0.5 | 0.15 |
| SD: standard deviation; GDS: Geriatric Depression Scale Short Form | | | |

Table 2. Prevalence of symptoms between groups

| | Group 1, patients (%) | Group 2, patients (%) | p |
|--|--------------------------------------|--------------------------------------|----------|
| Tremor | 88.9 | 89.2 | |
| Bradykinesia | 76.2 | 89.2 | |
| Pain-cramp | 58.7 | 70.3 | |
| Slowing gait | 55.6 | 70.3 | |
| Constipation | 55.6 | 56.8 | |
| EDS | 55.6 | 64.9 | |
| RBD | 50.8 | 54.1 | |
| Depression | 50.8 | 45.9 | |
| Fatigue | 47.6 | 70.3 | 0.02* |
| Anosmia | 44.4 | 29.7 | |
| Hyperhidrosis | 42.9 | 43.2 | |
| Polypharmacy | 41.3 | 45.9 | |
| Decreased libido/sexual function | 39.7 | 29.7 | |
| Frequent voiding/incontinence | 39.7 | 54.1 | |
| Recognition of tremor by others | 39.7 | 29.7 | |
| RLS | 36.5 | 37.8 | |
| Spasms | 31.7 | 43.2 | |
| Micrography | 25.4 | 18.9 | |
| Falling | 17.5 | 37.8 | 0.02* |
| Dyskinesia | 4.8 | 24.3 | 0.004** |
| EDS: Excessive daytime sleepiness; RBD: REM sleep behavior disorder; RLS: restless legs syndrome | | | |

havior disorder (54.1%), frequent voiding/incontinence (54.1%), polypharmacy (45.9%), hyperhidrosis (43.2%), spasm (43.2%), and restless legs syndrome (37.8%) were more common in Group 2 (Table 2).

The most disturbing symptoms affecting QoL in group 1 were reported to be tremor (30.2%), frequent voiding/incontinence (17.5%), bradykinesia (14.3%), decreased libido/sexual function (12.7%), and slow gait (11.1%). When the levels of disturbance of the symptoms were rated, those listed among the top three most disturbing symptoms were tremor (69.9%), bradykinesia (52.4%), slow gait (39.7%), frequent voiding/incontinence (27.1%), and decreased libido/sexual function (20.6%) (Table 3). Analysis of the occurrence of symptoms showed that the top three motor symptoms which disturbed QoL, i.e., tremor, bradykinesia, and slow gait, were the most common symptoms in this group. Pain-cramp (58.7%), constipation (55.6%), and EDS (55.6%), the most frequent non-motor symptoms, were symptoms that least disturbed QoL (17.5%, 17.4%, and 6.4%, respectively). In contrast, frequent voiding/incontinence (39.7%) and decreased libido/sexual function (39.7%), less common symptoms, were the non-motor symptoms that most disturbed QoL (27.1% and 20.6% respectively).

The most disturbing symptoms affecting QoL in group 2 were reported to be tremor (21.6%), bradykinesia (18.9%), frequent voiding/incontinence (13.5%), falling (13.5%), and slow gait (11.1%). When the levels of disturbance of the symptoms were rated, those listed among the

Table 3. Effects of symptoms on quality of life and their orders in group 1

| | First order, % | Second order, % | Third order, % | Frequency of being in the first three orders, % |
|--|-------------------------------|--------------------------------|-------------------------------|--|
| Tremor | 30.2 | 27 | 12.7 | 69.9 |
| Bradykinesia | 14.3 | 20.6 | 17.5 | 52.4 |
| Slowing gait | 11.1 | 15.9 | 12.7 | 39.7 |
| Frequent voiding/ incontinence | 17.5 | 4.8 | 4.8 | 27.1 |
| Decreased libido/ sexual functions | 12.7 | 1.6 | 6.3 | 20.6 |
| Recognition of tremor by others | 3.2 | 11.1 | 4.8 | 19.1 |
| Pain-cramps | 3.2 | 3.2 | 11.1 | 17.5 |
| Constipation | 1.6 | 9.5 | 6.3 | 17.4 |
| Depression | 1.6 | 3.2 | 7.9 | 12.7 |
| Falling | 4.8 | 4.8 | 1.6 | 11.2 |
| Hyperhidrosis | 1.6 | 1.6 | 6.3 | 9.5 |
| EDS | 0 | 1.6 | 4.8 | 6.4 |
| Polypharmacy | 0 | 4.8 | 1.6 | 6.4 |
| RBD | 0 | 0 | 4.8 | 4.8 |
| Dyskinesia | 1.6 | 0 | 1.6 | 3.2 |
| Spasms | 3.2 | 0 | 0 | 3.2 |
| Anosmia | 0 | 1.6 | 1.6 | 3.2 |
| Fatigue | 1.6 | 0 | 1.6 | 3.2 |
| RLS | 0 | 0 | 1.6 | 1.6 |
| Micrography | 0 | 0 | 0 | 0 |
| EDS: Excessive daytime sleepiness; RBD: REM sleep behavior disorder; RLS: restless legs syndrome | | | | |

top three most disturbing symptoms were bradykinesia (56.7%), tremor (51.3%), frequent voiding/incontinence (37.0%), slow gait (35.4%), and falling (18.9%) (Table 4). Analysis of the occurrence of symptoms revealed that bradykinesia and tremor, the two motor symptoms with the greatest impact on QoL, were the most common symptoms in this group. Frequent voiding/incontinence (54.1%), the 4th most common non-motor symptom, was the most disturbing to QoL. Pain-cramp (70.3%), fatigue (70.3%), and EDS (64.9%), the most frequent non-motor symptoms, were the symptoms that least disturbed QoL (16.2%, 8.1%, and 4.8%, respectively).

DISCUSSION

This study investigated the prevalence of motor and non-motor symptoms in IPD and the relative impact of these symptoms on QoL. Numerous studies have evaluated the effects of non-motor symptoms on the QoL of IPD patients. However, only limited data are available that assess motor and non-motor symptoms together and determine which symptoms are the most disturbing based on subjective patient reports.

There were no differences between the two groups, which were stratified as early or late disease by disease duration, in terms of sociodemo-

Table 4. Effect of symptoms on quality of life and their orders in group 2

| | First order, % | Second order, % | Third order, % | Frequency of being in the first three orders, % |
|----------------------------------|-----------------------|------------------------|-----------------------|--|
| Tremor | 21.6 | 27 | 2.7 | 51.3 |
| Bradykinesia | 18.9 | 13.5 | 24.3 | 56.7 |
| Frequent voiding/incontinence | 13.5 | 10.8 | 13.5 | 37 |
| Slowing gait | 11.1 | 5.4 | 18.9 | 35.4 |
| Falling | 13.5 | 5.4 | 0 | 18.9 |
| Pain-cramp | 2.7 | 5.4 | 8.1 | 16.2 |
| Constipation | 8.1 | 8.1 | 0 | 16.2 |
| Decreased libido/sexual function | 5.4 | 5.4 | 2.7 | 13.5 |
| Depression | 2.7 | 2.7 | 8.1 | 13.5 |
| Hyperhydrosis | 0 | 2.7 | 10.8 | 13.5 |
| Recognition of tremor by others | 2.7 | 0 | 5.4 | 8.1 |
| Spasm | 0 | 2.7 | 5.4 | 8.1 |
| Fatigue | 0 | 8.1 | 0 | 8.1 |
| RLS | 2.7 | 0 | 2.7 | 5.4 |
| EDS | 2.7 | 2.7 | 0 | 4.8 |
| RBD | 2.7 | 2.7 | 0 | 4.8 |
| Dyskinesia | 2.7 | 2.7 | 0 | 4.8 |
| Polypharmacy | 0 | 0 | 2.7 | 2.7 |
| Anosmia | 0 | 0 | 0 | 0 |
| Micrography | 0 | 0 | 0 | 0 |

EDS: Excessive daytime sleepiness; RBD: REM sleep behavior disorder; RLS: restless legs syndrome

graphic characteristics (age, gender, and level of education), GDS, and dopaminergic therapies; therefore, these factors appeared to be less likely to confound our findings.

We believe that questioning the patients' symptoms and separately asking them to rate the disturbance levels of said symptoms may offer an objective assessment regarding the prevalence and impact of symptoms on QoL.

Motor and non-motor symptoms are seen together from the earliest stages of the disease. However, their presence and severity vary over the course of the disease (10,11). Therefore, their impact on QoL also varies over the course of the disease. A study on early-term PD reported that non-motor symptoms were more deterministic than motor symptoms in terms of their potential effects on QoL (12). Although motor symptoms were the most common and most QoL-disturbing symptoms both in early-disease and late-disease patients, non-motor symptoms were commonly seen in both groups and negatively affected QoL, albeit less than motor symptoms. These findings imply that motor symptoms are still the most influencing symptoms for IPD patients. The impact of these symptoms on their daily activities may be pronounced. In fact, motor symptoms, when severe, are reported to impair the QoL

of patients (13). IPD was perceived to consist of motor symptoms, and existing non-motor symptoms were less attributed to the disease by their sufferers. If patients focus on motor symptoms, this may lead them to rank these symptoms highest in terms of QoL disturbance.

Because the broad spectrum of non-motor symptoms requires complicated study designs, only a few prevalence studies examining all non-motor symptoms have been performed, although copious research focuses on specific manifestations such as depression, cognitive disorder, or sleep disturbances (4). The first international prevalence study reported a higher prevalence of non-motor symptoms in IPD patients compared to age-matched controls, as well as the presence of 10-12 non-motor symptoms in a typical patient (14). A recent international and prospective prevalence study also found non-motor symptoms to be present in 98.6% of patients (15). In our study, non-motor symptoms were found to be frequent in both early-disease and late-disease patients. The most common symptoms in both studies were fatigue, pain, and sleep disturbance. Pain and EDS were frequent in both groups in our study. While also common in early-disease patients, fatigue was significantly more common in late-disease patients. In a study consisting of early, treatment-naïve IPD patients without depression and dementia, 34% of patients complained of fatigue, which was found to be associated with disease severity (16). In fact, fatigue was shown to impair QoL in IPD patients (17). Though common in both groups, fatigue was found to be less disturbing to QoL than other non-motor symptoms.

The prevalence of EDS has been reported to be 15%-32% in Parkinson's disease (PD) patients (18,19). In our study, the prevalence of EDS was found to be 55.6% in early-disease patients and 64.8% in late-disease patients, according to subjective patient assessments. Although it was frequently reported, EDS was also among the less disturbing symptoms to QoL in both groups. EDS has been reported to cause impaired attention and memory, resulting in fatal accidents (20). Therefore, it is important to recognize and manage this symptom despite its less dramatic impact on the QoL of patients.

In a study where the prevalence of pain was investigated in PD patients, 53% of patients reported pain that was not associated with disease severity or duration (21). In our study, pain was the most common non-motor symptom in both groups (58.7% in group 1 and 70.3% in group 2). In fact, when we analyzed the impact of non-motor symptoms on QoL, pain was the most commonly reported non-motor symptom after bladder and sexual dysfunction in early-disease patients and after bladder dysfunction in late-disease patients. For this reason, it is critical to question pain in IPD patients and manage it appropriately to improve their QoL.

Bladder and sexual dysfunction are frequent non-motor symptoms in IPD patients (22,23). In a study of early-disease patients, over 80% of patients reported frequent voiding and nocturia, around 60% reported urgency, and 43% reported urinary incontinence (24). Another study reported bladder dysfunction to be among the most common non-motor symptoms of the disease (25). Sexual dysfunction was detected in 73.5% of IPD patients; men were more likely to complain that this symptom disturbed QoL (26). Although they were not listed among

the most common non-motor symptoms in our study, bladder and sexual dysfunction were found to be the most QoL-disturbing non-motor symptoms in early-disease patients; in late-disease patients, bladder dysfunction was the most disturbing symptom. Previous literature studies confirmed the pronounced effects of these disorders on QoL; however, they showed that these symptoms were not frequently reported unless questioned by the physician (17).

Probably due to its initiation before the symptomatic phase of the disease, constipation is usually not attributed to IPD and is not mentioned by the patient unless asked. In our study, 55.6% and 56.8% of early-disease and late-disease patients respectively, described constipation, supporting the common prevalence of this symptom in both phases. Because of its substantial effects on QoL in both early-disease and late-disease patients, this symptom should be questioned in all patients and treated accordingly, if present.

Scoring systems have been developed to determine motor and non-motor symptoms and analyze QoL in IPD patients. It is possible that the lack of a scoring system in this study causes some limitation in comparing the results. However, we wanted to emphasize the patients' own expressions to determine the impact of their symptoms on QoL. Our questionnaire, which contains both motor and non-motor symptoms, seemed to enable patients to score and rate the disturbance levels of all their symptoms simultaneously.

In conclusion, it is widely accepted that motor symptoms determine QoL in IPD. However, non-motor symptoms are seen during all phases of the disease. The impact of non-motor symptoms on the QoL of IPD patients remains substantial. Therefore, in addition to the well-known motor symptoms, non-motor symptoms that may be overlooked during physical examination yet which profoundly impact QoL should be questioned and treated appropriately to improve QoL in IPD patients as greatly as possible.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Bezmialem Vakıf University School of Medicine.

Informed Consent: Verbal informed consent was obtained from all patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - G.B.Y., R.S.; Design - E.G., V.E.G., R.S.; Supervision - G.B.Y., T.A.; Resources - E.G., V.E.G.; Materials - E.G., V.E.G., R.S.; Data Collection and/or Processing - E.G., V.E.G., R.S.; Analysis and/or Interpretation - E.G., V.E.G., R.S.; Literature Search - E.G., V.E.G.; Writing Manuscript - E.G., V.E.G.; Critical Review - G.B.Y., T.A.; Other - R.S.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

- Pringsheim T, Jette N, Frolkis A, Steeves TD. The prevalence of Parkinson's disease: a systematic review and meta-analysis. *Mov Disord* 2014;29:1583-1590. [CrossRef]
- Zgaljardic DJ, Foldi NS, Borod JC. Cognitive and behavioral dysfunction in Parkinson's disease: neurochemical and clinicopathological contributions. *J Neural Transm* 2004;111:1287-1301. [CrossRef]
- Lohle M, Storch A, Reichmann H. Beyond tremor and rigidity: non-motor features of Parkinson's disease. *J Neural Transm* 2009;116:1483-1492. [CrossRef]
- Chaudhuri KR, Odin P, Antonini A, Martinez-Martin P. Parkinson's disease: the non-motor issues. *Parkinsonism Relat Disord* 2011;17:717-723. [CrossRef]
- Chaudhuri KR, Prieto-Jurcynska C, Naidu Y, Mitra T, Frades-Payo B, Tluk S, Ruessmann A, Odin P, Macphee G, Stocchi F, Ondo W, Sethi K, Schapira AH, Martinez Castrillo JC, Martinez-Martin P. The nondeclaration of non-motor symptoms of Parkinson's disease to health care professionals: an international study using the nonmotor symptoms questionnaire. *Mov Disord* 2010;25:704-709. [CrossRef]
- Bernheim J. Improving the quality of life and survival of cancer patients. *Rev Med Liege* 1984;39:122-126.
- MacKeigan LD, Pathak DS. Overview of health-related quality-of-life measures. *Am J Hosp Pharm* 1992;49:2236-2245.
- Cella DF. Measuring quality of life in palliative care. *Semin Oncol* 1995;22(Suppl 3):73-81.
- Gelb DJ, Oliver E, Gilman S. Diagnostic criteria for Parkinson disease. *Arch Neurol* 1999;56:33-39. [CrossRef]
- Tolosa E, Gaig C, Santamaria J, Compta Y. Diagnosis and the premotor phase of Parkinson disease. *Neurology* 2009;72(Suppl 7):S12-20. [CrossRef]
- Muller B, Larsen JP, Wentzel-Larsen T, Skie GO, Tysnes OB, Parkwest Study G. Autonomic and sensory symptoms and signs in incident, untreated Parkinson's disease: frequent but mild. *Mov Disord* 2011;26:65-72. [CrossRef]
- Muller B, Assmus J, Herlofson K, Larsen JP, Tysnes OB. Importance of motor vs. non-motor symptoms for health-related quality of life in early Parkinson's disease. *Parkinsonism Relat Disord* 2013;19:1027-1032. [CrossRef]
- Visser M, Verbaan D, van Rooden S, Marinus J, van Hilten J, Stiggelbout A. A longitudinal evaluation of health-related quality of life of patients with Parkinson's disease. *Value Health* 2009;12:392-396. [CrossRef]
- Chaudhuri KR, Martinez-Martin P, Schapira AH, Stocchi F, Sethi K, Odin P, Brown RG, Koller W, Barone P, MacPhee G, Kelly L, Rabey M, MacMahon D, Thomas S, Ondo W, Rye D, Forbes A, Tluk S, Dhawan V, Bowron A, Williams AJ, Olanow CW. International multicenter pilot study of the first comprehensive self-completed nonmotor symptoms questionnaire for Parkinson's disease: the NMSQuest study. *Mov Disord* 2006;21:916-923. [CrossRef]
- Barone P, Antonini A, Colosimo C, Marconi R, Morgante L, Avarello TP, Bot-tacchi E, Cannas A, Ceravolo G, Ceravolo R, Cicarelli G, Gaglio RM, Giglia RM, Iemolo F, Manfredi M, Meco G, Nicoletti A, Pederzoli M, Petrone A, Pisani A, Pontieri FE, Quatrala R, Ramat S, Scala R, Volpe G, Zappulla S, Bentivoglio AR, Stocchi F, Trianni G, Dotto PD, group Ps. The PRIAMO study: A multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. *Mov Disord* 2009;24:1641-1649. [CrossRef]
- Schiffitto G, Friedman JH, Oakes D, Shulman L, Comella CL, Marek K, Fahn S, Parkinson Study Group El. Fatigue in levodopa-naïve subjects with Parkinson's disease. *Neurology* 2008;71:481-485. [CrossRef]
- Gallagher DA, Lees AJ, Schrag A. What are the most important nonmotor symptoms in patients with Parkinson's disease and are we missing them? *Mov Disord* 2010;25:2493-2500. [CrossRef]
- Arnulf I, Bonnet AM, Damier P, Bejjani BP, Seilhean D, Derenne JP, Agid Y. Hallucinations, REM sleep, and Parkinson's disease: a medical hypothesis. *Neurology* 2000;55:281-288. [CrossRef]
- Hobson DE, Lang AE, Martin WR, Razmy A, Rivest J, Fleming J. Excessive daytime sleepiness and sudden-onset sleep in Parkinson disease: a survey by the Canadian Movement Disorders Group. *JAMA* 2002;287:455-463. [CrossRef]
- Ondo WG, Dat Vuong K, Khan H, Atassi F, Kwak C, Jankovic J. Daytime sleepiness and other sleep disorders in Parkinson's disease. *Neurology* 2001;57:1392-1396. [CrossRef]

21. Lin XJ, Yu N, Lin XG, Zhang YF, Chen Y, Zhang K, Wang XS, Liu WG. A clinical survey of pain in Parkinson's disease in Eastern China. *Int Psychogeriatr* 2016;28:283-289. [\[CrossRef\]](#)
22. Aarsland D, Andersen K, Larsen JP, Lolk A, Nielsen H, Kragh-Sorensen P. Risk of dementia in Parkinson's disease: a community-based, prospective study. *Neurology* 2001;56:730-736. [\[CrossRef\]](#)
23. Factor SA, McAlarney T, Sanchez-Ramos JR, Weiner WJ. Sleep disorders and sleep effect in Parkinson's disease. *Mov Disord* 1990;5:280-285. [\[CrossRef\]](#)
24. Verbaan D, Marinus J, Visser M, van Rooden SM, Stiggelbout AM, van Hilten JJ. Patient-reported autonomic symptoms in Parkinson disease. *Neurology* 2007;69:333-341. [\[CrossRef\]](#)
25. O'Sullivan SS, Williams DR, Gallagher DA, Massey LA, Silveira-Moriyama L, Lees AJ. Nonmotor symptoms as presenting complaints in Parkinson's disease: A clinicopathological study. *Mov Disord* 2008;23:101-106. [\[CrossRef\]](#)
26. Mott S, Kenrick M, Dixon M, Bird G. Sexual limitations in people living with Parkinson's disease. *Australas J Ageing* 2005;24:196-201. [\[CrossRef\]](#)