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Sexual Dysfunction in Parkinson Disease: A Multicenter Italian Cross-sectional Study on a Still Overlooked Problem

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ABSTRACT

Background: Prevalence rates of sexual dysfunction (SD) in Parkinson's disease (PD) are likely to be underestimated and their etiology is still unknown. More understanding of this issue is needed.

Aim: To investigate prevalence of SD and its variables, including gender differences, in a sample of PD patients.

Methods: This multicenter observational study included 203 patients (113 males and 90 females) affected by PD (diagnosed according to UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria 28), and living in 3 different Italian regions. Patients were evaluated using a semi-structured interview (a 40-item ad hoc questionnaire, developed by the authors to investigate patient's 3 main life areas: sociodemographic information, illness perception, and sexuality) and specific standardized scales to investigate SD, as well as by means of tools to assess their motor impairment, daily life activities, and disease-related caregiver burden (CBI).

Main Outcome Measures: The International Index of Erectile Function and the Female Sexual Function Index.

Results: Sexual dysfunction was observed in about 68% of men, and in around 53% of women loss of libido being the main sexual concern in both sexes. Men were significantly more affected by SD than women (χ^2 (1) = 4.34, *P*-value = .037), but no difference in the severity of the dysfunction emerged between genders. Around 85% of PD patients had a stable couple relationship, and about 40% were satisfied with such a relationship. However, about 57% of the patients stated that the disease affected their sexual life, especially due to reduced sexual desire, and the frequency of sexual intercourses. Moreover, significant differences between subjects with SD and subjects without SD were found in UPDRS (I-II-III domains), in Hamilton Depression Rating Scale and CBI scores.

Clinical Implications: Clinicians dealing with PD should pay more attention to sexual issues, as discussing and treating sexual problems enters the framework of a holistic approach, which is mandatory in chronic illness.

Strengths & Limitations: The major strengths of this study include the multicenter nature of the study, to overcome single-center methodological bias. The main limitation is the relatively small sample size, and the absence of a control group, even if there are growing literature data on sexuality and aging supporting our findings.

Conclusion: SD is a highly prevalent and devastating problem in patients affected by PD, negatively affecting their quality of life. **Raciti L, De Cola MC, Ortelli P, et al. Sexual Dysfunction in Parkinson Disease: A Multicenter Italian Cross-sectional Study on a Still Overlooked Problem. J Sex Med 2020;XX:XXX–XXX.**

Key Words: Erectile Dysfunction; Anorgasmia; Dopaminergic Drugs; Neurodegenerative Disorders; Quality of Life

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INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disease involving the *pars compacta* of the *substantia nigra*, leading to dopamine deficiency phenotypically manifesting as resting tremor, rigidity, bradykinesia, and gait shuffling, which are the main motor manifestations of the disease.[1,2]

In the last few years, clinical and epidemiological studies have focused on the importance of nonmotor symptoms (NMS) and gender differences in influencing quality of life, as well as progression and therapeutic response of Parkinson's disease patients.[3,4] NMS features can precede PD motor symptoms by many years and, among them, urinary symptoms, with regard to nocturia and urinary urgency, were recognized in 61.9% and 55.8% of PD patients, respectively. Cognitive, autonomic (orthostatic hypotension, constipation), sexual (mainly hypoactive desire and erectile dysfunction, ED), and sleep problems (ie, REM sleep behavior disorder), depression, and hyposmia were instead reported in about 30% of the patients, by using the NMSS questionnaire, a useful instrument for the assessment of the frequency and the severity of such symptoms in PD.[5−8] Sexual dysfunction (SD) in PD include ED, premature ejaculation, orgasm difficulties, and decreased libido in men, whilst decreased libido and difficulties in reaching orgasm are the most common SD in women.[9] However, the prevalence rates of SD in PD are likely to be underestimated and etiology is still unknown, due to an embarrassment of the patient in reporting SD or to a not exhaustively investigation by the physician. In fact, neither the recent Movement Disorders Society−Unified Parkinson's Disease Rating Scale (UPDRS)[10] includes any item on sexual function nor the most commonly used quality of life questionnaire, the PDQ-39,[11] whereas only 2 items on such important issue (ie, alteration in sexual interest and presence of problems having sex without any reference to overall sexual functioning) are included in the Non-Motor Symptom assessment scale (NMS-Q) for PD.[12] Also, the SCOPA-AUT has got 2 items concerning ED and ejaculation in men and vaginal dryness and orgasm in women. However, no questions concerning patients' sexual satisfaction, partner's sexual function and satisfaction, and the quality of the couple's relationship are evaluated by the present tools.[13] On the other hand, recently a screening instrument to evaluate hypersexuality in patients with PD has been developed.[14]

As compared to men, few studies are available concerning female SD in PD and data are still controversial.[15] As reported by Zhao et al in their meta-analysis, 3 studies reported nonsignificant reduction in sexual functioning in women with PD, as compared with the general population (RR = 1.3, 95% CI = 0.64-2.61, P = .469). However, the risk for specific sexual problems, as a decrease in libido, is still debating due to the contrasting results.[16] Also, gender differences in the prevalence of quality of sexual life in PD have led to ambiguous results.[17,18] Thus, more research is needed to better investigate this important issue.

The prevalence of SD in PD ranges from 42.6% to 79% in male subjects and from 36% to 87.5% in females,[19] demonstrating how gender plays an important role in the expression of PD. In fact, men are at higher risk of developing PD with an age-standardized incidence M:F ratio of 1.46 (95% CI 1.24−1.72).[15,20] Several studies showed that reduced interest in sex and problems in having sex are more prevalent in men.[20] In addition, men with ED have a 3.8 higher risk of developing PD, as compared to controls.[19] Nevertheless, several studies failed to demonstrate a risk of SD in patients with PD compared to healthy controls.[14,21−23]

A recent meta-analysis of 30.150 individuals (5.437 of whom with PD) has shown that PD is associated with an elevated risk of SD in males (7 studies; 1.79; 95% CI = 1.26-2.54, P = .001), as compared to healthy control. On the contrary, in females with PD, this high risk was not found.[24] This gender difference could be explained by sex hormones, as the higher exposure to endogenous and exogenous estrogens in females seems to be a protective factor, by avoiding the dopaminergic neuron depletion caused.[25,26] The dopaminergic effect on SD is still under debate. Patients treated with dopaminergic therapy, such as dopaminogonists, could experience a dopamine dysregulation syndrome which causes hypersexuality and compulsive sexual behavior. However, there could be a contextual presence of ED leading to lack of orgasm.[27−30]

The aim of this study was to evaluate the prevalence of SD in a multicenter study involving both male and female patients with PD, by using a specific semi-structured interview developed by the authors, as well as standardized sexual scales. In particular, we sought to investigate how gender differences and other variables, including age, marital status, comorbidity, depression, and PD medications, may affect sexuality in this neurological population.

Results collected from this cross-sectional study may furnish the basis for future randomized clinical studies which will investigate the etiology of SD while taking into account the important gender differences.

MATERIAL AND METHODS

Study Design and Settings

This is a multicenter cross-sectional study, and participants were recruited from 3 different Italian centers, that is, the IRCCS "Centro Neurolesi Bonino-Pulejo" (located in Sicily), the "Fondazione Centri di Riabilitazione Gli Angeli di Padre Pio" (located in Puglia), and the Ospedale Motiggia Pelascini (situated in Lombardy) who underwent specific neurological and sexological tests, administered by skilled health care professionals. The study was approved by the Local Ethics Committees for Clinical Research.

Study Population

The study sample included 203 patients (113 males and 90 females) affected by PD according to UK Parkinson's Disease

Society Brain Bank clinical diagnostic criteria,[31] living in 3 different Italian regions. Inclusion criteria were as follows: age between 60 and 80 years, and a Hoehn-Yahr stage 1-3.[32,33] Patients were excluded if they had moderate to severe cognitive decline (MMSE <16)[34] and/or severe medical and psychiatric disorders, or sensory deficits potentially interfering with the assessment completion.

Clinical, Psychological, and Sexual Assessment

The Unified Parkinson's Disease Rating Scale (UPDRS)[33] was used to evaluate the impact of Parkinson's on patients' daily life activities, besides their motor impairment.

Emotional status was tested using the Hamilton Depression Rating Scale (HAM-D),[35] a 17- to 21-item scale measuring the severity of depressive and somatization symptoms, where a score of ≥15 is generally regarded as indicative of a diagnosis of depression.

The Caregiver Burden Inventory (CBI)[36] was used to investigate the level of burden on 5 different domains of caregiving: time-dependence, developmental, physical, social, and emotional burden. Each item was given a score between 0 and 4, where higher scores indicate greater caregiver burden; there were no cutoff points for classifying burden.

Sexual function was clinically assessed by a semi-structured interview, the International Index of Erectile Function (IIEF),[37] the Female Sexual Function Index (FSFI),[38,39] and the Diagnostic Impotence Questionnaire (DIQ).[40]

The International Index of Erectile Function (IIEF)[37] is a validated, multidimensional, self-report instrument widely used as "gold standard" tool for male sexual dysfunction, especially erectile dysfunction (ED). IIEF is a semi-structured interview that contains 15 questions about the patients' sexual experiences over the preceding 4 weeks. Questions were ranked on a 5-point scale, and patient erectile function was found by totaling the number of points in the survey and subdivided into 5 separate domains of sexual function: (1) erectile function, (2) orgasmic function, (3) sexual desire, (4) intercourse satisfaction, and (5) overall satisfaction. Domain scores were computed by summing the scores for individual items in each domain. The IIEF has a high degree of sensitivity and specificity. The optimal cutoff score was found to be 25, with men scoring less than or equal to 25 classified as having ED.[37]

On the other hand, the Female Sexual Function Index (FSFI)[38] is a widely used measure of female sexual dysfunction (FSD). It measures 6 domains: desire; arousal; lubrication; orgasm; satisfaction; and pain with an excellent internal consistency and 2- to 4-week test-retest reliability for each subscale. A cutoff total score of ≤26.55 has been proposed for diagnosis of female SD.[38,39]

Finally, the Diagnostic Impotence Questionnaire (DIQ)[40] is a 35-item test that evaluates the features of erectile dysfunction as vascular, neurogenic, hormonal, or psychogenic origin. If the psychogenic score is lower than the total of the other 3 component scores, the organic etiology is predominant. Although the questionnaire is useful in the clinical practice, the scale is not valid or standardized.[40]

The semi-structured interview is a 40-item ad hoc questionnaire, developed by the authors, that investigates patient's 3 main life areas: sociodemographic information, illness perception, and sexuality.[41] The information collected includes sex, age, educational level, employment, marital status, religion, number of children, onset and disease duration, disease-modifying therapy, degree of relationship (job, family, and love satisfaction), and quality of life satisfaction (using a 5-point scale). Also, the tool explores several aspects of a patient's past and present sexual life (assessing 3 specific periods related to the disease: "before diagnosis," "after PD diagnosis," and "after the PD drug administration use"), such as sexual activity, masturbation, kind and frequency of sexual intercourse, sexual relationship satisfaction. We decided to use this "ad hoc" interview to have more information on the disease-related sexual life and on patient's relationships and satisfaction, as the main validated tools lack of this specific issue.

To avoid nonresponse and to be sure that all questions were comprehensible, when the patients were unable or unwilling to complete the questionnaire, we read and explained the questions as clearly as possible. We accurately reported their answer if strictly necessary. It is noteworthy mentioning that the questionnaires were administered by local psychologists who were familiar with the native language and habits of the patients.

Statistical Analysis

Statistical analysis was performed by using the 3.5.0 version of the open-source software R, considering a $P < .05$ as the level of significance. Continuous variables were presented as mean ± standard deviation, whereas categorical variables as frequencies and percentages. Normality of distribution was assessed by using the Shapiro–Wilk test. In presence of not normal data distribution, nonparametric statistical tests were used and continuous variables were presented as median (first-third quartile). Thus, the Wilcoxon rank-sum test was used to compare continuous variables, whereas the X^2 test with continuity correction was used to assess for statistical differences in proportions.

The semi-structured interview contained ten multiple-choice questions aimed to retrospectively collect information concerning the patient sexual life before-after the diagnosis and before-after the beginning of the drug treatment for the disease. Thus, these questions were codified in ordinal variables at 3 different times (T0 = pre-illness; T1 = pre-treatment; T2 = post-treatment) and the Friedman test was used to perform over time comparisons. Correlations were performed by the Spearman's rank correlation coefficient.

Table 1. Demographic description of the sample

Characteristics	All	Males	Females	*P*-value
Participants	203	113 (55.67)	90 (44.33)	-
Age (years)	68.36 ± 8.5	68.52 ± 8.65	68.15 ± 8.35	.63
Education				**< .01**
None	15 (7.39)	1 (0.88)	14 (15.55)	
Elementary school	62 (30.54)	32 (28.32)	30 (33.33)	
Middle school	56 (27.59)	37 (32.74)	19 (21.11)	
Vocational school	35 (17.24)	20 (17.70)	15 (16.67)	
High school	18 (8.87)	13 (11.51)	5 (5.56)	
University degree	17 (8.37)	10 (8.85)	7 (7.78)	
Marital status				.23
Single	4 (1.97)	3 (2.65)	1 (1.11)	
Married	170 (83.74)	99 (87.61)	71 (78.89)	
Living with partner	4 (1.97)	2 (1.77)	2 (2.22)	
Separated	3 (1.48)	2 (1.77)	1 (1.11)	
Divorced	7 (3.45)	3 (2.65)	4 (4.45)	
Widowed	15 (7.39)	4 (3.54)	11 (12.22)	
Children				.41
None	7 (3.45)	2 (1.77)	5 (5.56)	
Yes, with the current partner	171 (84.24)	96 (84.96)	75 (83.33)	
Yes, with the previous partner	23 (11.33)	13 (11.50)	10 (11.11)	
Other	2 (0.98)	2 (1.77)	0 (0.00)	

Continuous variables were expressed as mean ± standard deviation, whereas categorical variables as frequencies and percentages. Significant differences are in bold.

Finally, a multiple logistic regression was performed to assess possible predictors of sexual dysfunction among clinical (type of pharmacological treatment, depression, comorbidity) variables and demographics (age, gender, marital status). We applied a backward elimination stepwise procedure for the choice of the best predictive variables according to the Akaike information criterion (AIC).[42]

RESULTS

Demographics and Clinical Features

Patients' mean age was 68.36 ± 8.5 years with a mean disease duration of 7.78 ± 5.77 years. A detailed demographic and clinic description of the patients is reported in Tables 1–2.

The sample was homogeneous with regards to gender and included patients with a medium-low level of education, mainly married with children. Among the 178 patients treated with drugs, 53.93% were treated with levodopa, 6.17% dopamine agonists, and about 40% were on mixed treatments. About 30% of the patients were under antidepressants/anxiolytics, and another 30% took antihypertensive drugs. Sexual dysfunction was observed in about 68% of men, and in around 53% of women being loss of libido the main sexual concern in both sexes. Men were significantly more affected by SD than women (χ^2 (1) = 4.34, *P*-value = .037), but no gender difference in the severity of dysfunction emerged (Table 2).

The age of patients correlated with HAM-D (r = 0.23, $P < .001$), FSFI (r = - 0.38, $P < .001$), and CBI (r = 0.35, $P < .001$). Similarly, the H-Y score correlated with HAM-D (r = 0.30, $P < .001$) and CBI (r = 0.48, $P < .001$): the higher the stage of the disease, the higher the depression of the patient and the burden of the caregiver. As shown in Table 3, we found a significant difference in UPDRS-IV scores between men and women ($P = .04$). Statistically significant differences between subjects with comorbidity and subjects without comorbidity were found in UPDRS-I ($P < .01$), UPDRS-II ($P = .03$), and HAM-D ($P < .01$) scores.

Diagnosis Communication and Changes in Relationships

Several reactions to the disease's diagnosis have been reported, that is, resignation (16.75%), discouragement (6.4%), sadness (13.3%), denial (7.39%), fear (11.33%), and depression (6.9%), but also indifference (11.33%), and anger (3.94%), without significant differences with regards to gender (χ^2 (12) = 12.83, *P*-value = .38). About half of the participants believe that their way of relating changed after the diagnosis, especially due to their sense of isolation (17.73%), aggression (8.87%), and apathy (4.93%). This result was confirmed by 33.5% of caregivers, who stated that the patient became more isolated, disinterested, and aggressive after the diagnosis.

With regards to the quality of life, 31.03% of the patients declared to be neither satisfied nor unsatisfied, 39.90% were satisfied or very satisfied, and 28.57% were unsatisfied or very

Table 2. Clinical description of the sample

Characteristics	All	Males	Females	*P*-value
Years of illness	7.78 ± 5.77	8.04 ± 5.89	7.45 ± 5.63	.38
Hoehn and Yahr score	2.59 (2.51)	2.45 ± 1.06	2.76 ± 3.53	.81
Diagnosis				.51
Parkinson's disease	197 (97.04)	108 (95.57)	89 (98.89)	
Parkinsonism	6 (2.96)	5 (4.43)	1 (1.11)	
Comorbidity				.99
None	49 (24.14)	27 (23.89)	22 (24.44)	
Hypertension	85 (41.87)	44 (38.94)	41 (45.56)	
Cardiopathy	35 (17.24)	22 (19.47)	13 (14.44)	
Diabetes	38 (18.72)	20 (17.70)	18 (20.00)	
Dyslipidemia	4 (1.97)	2 (1.77)	2 (2.22)	
Other	64 (31.53)	34 (30.09)	30 (33.33)	
Autonomic symptoms				.24
None	100 (49.26)	61 (53.98)	39 (43.33)	
Constipation	53 (26.11)	25 (22.12)	28 (31.11)	
Hypotension	5 (2.46)	4 (3.54)	1 (1.11)	
Other	7 (3.45)	3 (2.66)	4 (4.44)	
Not stated	38 (18.72)	20 (17.70)	18 (20.00)	
Drug for Parkinson				.55
None	25 (12.32)	17 (15.04)	8 (8.89)	
Levodopa	96 (47.29)	52 (46.02)	44 (48.89)	
Dopamine agonists	11 (5.42)	5 (4.43)	6 (6.67)	
Mixed	71 (34.98)	39 (34.51)	32 (35.55)	
Extra drugs				.29
None	85 (41.87)	52 (46.02)	33 (36.67)	
Antidepressants/anxiolytics	35 (13.79)	16 (14.16)	19 (21.11)	
Antihypertensive	34 (16.75)	16 (14.16)	18 (20.00)	
Antipsychotics	7 (3.45)	6 (5.31)	1 (1.11)	
Other	34 (16.75)	19 (16.81)	15 (16.67)	
Not stated	8 (3.94)	4 (3.54)	4 (4.44)	
Sexual dysfunction				.14
None	75 (38.46)	34 (31.48)	41 (47.13)	
Mild	19 (9.74)	13 (12.04)	6 (6.89)	
Moderate	42 (21.54)	25 (23.15)	17 (19.54)	
Severe	59 (30.26)	36 (33.33)	23 (26.44)	
Type of sexual dysfunction				**< .001**
Sexual desire reduction	80 (44.20)	44 (46.32)	36 (41.86)	
Sexual desire increase	25 (13.81)	17 (17.89)	8 (9.30)	
Erectile dysfunction	20 (11.05)	20 (21.05)	-	
Premature ejaculation	3 (1.66)	3 (3.16)	-	
Delayed ejaculation	1 (0.55)	1 (1.05)	-	
Anorgasmia	5 (2.76)	0 (0.00)	5 (5.81)	
Other	6 (3.32)	4 (4.21)	2 (2.32)	
Not stated	41 (22.65)	6 (6.32)	35 (40.31)	

Continuous variables were expressed as mean ± standard deviation, whereas categorical variables as frequencies and percentages. Significant differences are in bold.

unsatisfied. No significant differences between women and men in these satisfaction rates emerged.

Diagnosis and Treatment Effects on Sexuality

Around 85% of PD patients have a stable couple relationship, of whom 18.72% were satisfied and 38.42% very satisfied with such relationship. However, around 57% of the patients stated that the disease affected their sexual life, especially by reducing sexual desire (15.27%) and the frequency of sexual intercourses (13.8%).

As shown in Table 3, significant differences between subjects with SD and subjects without SD were found in UPDRS (I-II-III domains), in HAM-D and in CBI scores. Moreover, we found a

Table 3. Group comparisons of the clinical and psychological scale scores

Scale	Women median (first-third quartile)	Men median (first-third quartile)	*P*-value
UPDRS	82.00 (37.00–119.25)	71.00 (40.00–103.00)	.83
UPDRS-I	19.00 (6.75–26.00)	12.00 (6.00–22.00)	.24
UPDRS-II	20.50 (8.75–29.50)	18.00 (11.00–28.00)	.49
UPDRS-III	41.00 (16.00–61.00)	36.00 (22.00–51.00)	.91
UPDRS-IV	1.50 (0.00–6.00)	4.00 (0.00–8.00)	**.04**
HAM-D	15.50 (9.25–24.00)	15.00 (8.50–20.00)	.37
CBI	21.00 (7.00–42.50)	26.00 (3.00–48.00)	.84
Scale	Comorbidity median (first-third quartile)	None comorbidity median (first-third quartile)	*P*-value
UPDRS	82.00 (41.00–116.00)	51.50 (31.00–85.25)	**.02**
UPDRS-I	17.00 (7.00–26.00)	9.50 (2.00–15.00)	**< .01**
UPDRS-II	21.00 (10.50–30.00)	14.00 (7.00–20.00)	**.03**
UPDRS-III	41.00 (20.50–58.00)	30.00 (17.00–43.75)	.09
UPDRS-IV	3.00 (0.00–7.00)	3.00 (0.00–6.00)	.65
HAM-D	16.00 (10.00–23.00)	12.50 (6.00–17.25)	**< .01**
CBI	25.00 (7.00–48.00)	9.00 (0.00–37.00)	.05
FSFI	19.00 (12.75–27.00)	30.00 (15.00–38.00)	.06
IIEF	27.50 (14.25–36.50)	20.00 (10.50–28.50)	.28
DIQ	13.00 (4.00–25.00)	15.00 (14.00–16.50)	.68
Scale	Presence of SD median (first-third quartile)	Absence of SD median (first-third quartile)	*P*-value
UPDRS	81.00 (42.00–124.50)	55.00 (31.50–97.00)	**.01**
UPDRS-I	17.0 (7.00–26.00)	10.00 (3.00–20.00)	**< .01**
UPDRS-II	21.00 (13.00–34.00)	14.00 (7.00–22.00)	**< .01**
UPDRS-III	40.00 (22.50–58.50)	25.00 (15.50–50.00)	**.03**
UPDRS-IV	2.00 (0.00–6.00)	5.00 (0.00–8.00)	.15
HAM-D	17.00 (11.00–23.50)	13.00 (7.00–19.00)	**< .01**
CBI	31.50 (14.00–52.25)	8.00 (0.00–24.00)	**< .001**
DIQ	31.00 (17.50–31.00)	31.00 (28.25–31.00)	.07

Significant differences are in bold.
CBI = Caregiver Burden Inventory; DIQ = Diagnostic Impotence Questionnaire; FSFI = Female Sexual Function Index; HAM-D = Hamilton Depression Rating Scale; IIEF = International Index of Erectile Function; SD = sexual dysfunction; UPDRS = Unified Parkinson's Disease Rating Scale.

significant difference between these 2 classes also concerning age ($P < .001$), education ($P = .02$), and stage of the disease ($P < .01$): SD mainly affected poorly educated older men, with a higher stage of disease.

Sexual dysfunction was found in 120/203 patients, that is, about 60%. They were prevalently men (61.67%) and significantly older than the ones without SD ($P < .001$). According to the gender, the prevalence of SD was significantly higher ($\chi 2$ (1) = 4.34, *P*-value = .04) in males (68.52%) than in females (52.87%). The prevalence of SD in patients taking drugs for PD was 59.41%, whereas it was 75% in those not taking PD medications, but no significant difference emerged ($\chi 2$ (1) = 1.88, *P*-value = .17). On the contrary, the prevalence of SD in patients with comorbidities was 65.77% versus 47.83% in patients without comorbidities with a statistically significant difference ($\chi 2$ (1) = 4.05, *P*-value = .04). However, we found that only diabetes mellitus was significantly associated with a high prevalence of SD ($\chi 2$ (1) = 7.77, *P*-value < .01).

Men perceived their SD significantly worse than women ($\chi 2$ (1) = 7.17, *P*-value < .01), and they felt less attractive to the partner ($\chi 2$ (5) = 17.65, *P*-value < .01). About 35% of subjects declared having spontaneous excitement in the morning, and only 15.76% felt excitement during the execution of intimate hygiene. Only 25% admitted to have practiced masturbation before the diagnosis of PD (T0), and the frequency of masturbation was significantly different at T1 (pre-treatment) and T2 (post-treatment), as well as sexual activity and sexual problems decreased over time (see Table 4). However, the reduction of such activities was more evident between T0 and the introduction of the pharmacological treatment (T1). Indeed, if at T0 around 64.04% of patient had full sexual intercourses weekly, at T1, this sexual activity was reduced to 36.45%, and at T2 to

Table 4. Friedman's test results to compare within the group post-treatment (T2), pre-procedural (T1), and pre-illness (T0) sexual conditions (in bold, there are significant results)

Sexual environment	Test value	df	*P*-value
Masturbation	13.267	2	**.0013**
Sexual intercourse	141.00	2	**< .001**
Sexual problems	42.522	2	**< .001**

31.53%. On the contrary, the percentage of patients who had sex less than once a month was around 9.36% at T0, which increased to 31.64% at T1, and to 35.47% at T2. Similarly, sexual problem occurrence varied from 57.80% at T0 (SD were mostly episodic or sporadic events, 15.76%), to 76.09% at T1, and to 83.04% at T2, where they increasingly occurred permanently (33.5%). About 40% of the patients declared a reduction of the sexual desire. On the contrary, about 13% declared an increase in sexual desire, which resulted to be associated with the type of drug treatment (χ^2 (24) = 44.03, *P*-value < .01), that is, with levodopa or a mixed treatment.

We found an association between the type of SD and the gender (χ^2 (7) = 46.95, *P*-value < .001). Notably, only women reported anogarsmia (χ^2 (1) = 3.72, *P*-value = .04), even if 40.31% did not specify the type of SD. On the contrary, an association between the intake of medication for PD and the occurrence of erectile dysfunction in men emerged (χ^2 (1) = 8.77, *P*-value < .01), as well as an association between the absence of a concomitant disease and premature ejaculation (χ^2 (1) = 6.67, *P*-value = .01), as shown in Table 5.

Concerning the manner of dealing with sexual intercourse, about 35.46% of the sample declared of being calm and relaxed, 17.24% of being indifferent, and 30.06% declared a negative mood as frustration (11.33%), anxiety (9.36%), angry (5.91%), and fair (3.45%).

Finally, the backward elimination stepwise procedure identified the logistic model including as predictors age, gender, marital status, and depression. However, only age, gender, and depression resulted as significant predictors for SD, as reported in Table 6.

DISCUSSION

To the best of our knowledge, this is the first Italian cross-sectional multicenter study, based on a semi-structured interview and self-reported sexual questionnaires, aimed at evaluating the prevalence and gender difference of SD in PD and to identify the main variables that could have influenced SD over time. In addition, we have highlighted the importance of poorly investigated (especially in women) risk factors for SD in this neurological population, including psychosexual history and the perception of the sexual relationship.

Sexual dysfunction is a highly devastating problem in patients with neurological disorders, and it was reported as the 12th most bothersome of 24 symptoms in PD patients.[43] In our sample, SD was present in about 70% of male patients and in about 50% of women with a statistically significant difference between the 2 genders. However, no differences on severity of SD were found, in line with literature data. In a recent metanalysis, Zhao et al reported a 2-fold risk of SD in men with PD, as compared to healthy controls, and an average rate of SD in men with PD of 8.9% compared with the general populations (6.1%).[24] On the other hand, the study reported that female PD subjects did not demonstrate a higher prevalence of SD than the general population.[24] Also, a study by Martinez-Martin et al found a lower SD prevalence in women (about 28%) than in men with PD (about 50%).[44,45] The substantial difference seems to be related to diversity in nigrostriatal dopaminergic innervations, with higher levels of striatal dopamine transporter binding in women,

Table 5. Medications and comorbidity according to the type of sexual dysfunction

	Drugs for PD			Comorbidity		
Type of sexual dysfunction	Yes	No	*P*-value	Yes	No	*P*-value
Men	n = 96	n = 17		n = 86	n = 27	
Sexual desire reduction	41 (42.71)	3 (17.65)	.09	36 (41.86)	8 (29.63)	0.36
Sexual desire increase	15 (15.62)	2 (11.76)	.97	13 (15.12)	4 (14.81)	0.99
Erectile dysfunction	12 (12.50)	8 (47.06)	**< .01**	15 (17.44)	5 (18.52)	0.99
Premature ejaculation	2 (2.08)	1 (5.88)	.94	0 (0.00)	3 (11.11)	**0.01**
Delayed ejaculation	1 (1.04)	0 (0.00)	.99	1 (1.16)	0 (0.00)	0.99
Anorgasmia	0 (0.00)	0 (0.00)	-	0 (0.00)	0 (0.00)	-
Other	3 (3.12)	1 (5.88)	.99	4 (4.65)	0 (0.00)	0.59
Women	n = 82	n = 8		n = 68	n = 22	
Sexual desire reduction	31 (37.80)	5 (62.50)	.33	30 (44.12)	6 (27.27)	0.25
Sexual desire increase	8 (9.76)	0 (0.00)	.78	5 (7.35)	3 (13.64)	0.64
Anorgasmia	5 (6.10)	0 (0.00)	.99	1 (1.47)	1 (4.54)	0.98
Other	1 (1.22)	1 (12.50)	.42	1 (1.47)	1 (4.54)	0.98

Significant differences are in bold.

Table 6. Backward logistic regression: significant predictors of sexual dysfunction

Predictors	Odds ratio	Std. err.	Wald z	[95% conf.	interval]	*P*-value
Age	1.06	0.02	2.76	1.02	1.10	<.01
Gender - male	1.90	0.34	2.45	1.02	3.57	.04
Depression	1.04	0.02	2.23	1.01	1.08	.02

Pseudo-$R^2 = 0.28$; Prob > $\chi^2(8) < 0.001$.

as compared to men.[46] This could be a consequence of different sex hormone levels, given the neuroprotective role of estrogen in preventing the dopaminergic neuron depletion caused by neurotoxins in PD.[47]

Satisfaction in sexuality expression and life is the reverberation of a general good and satisfied quality of life (QoL) in PD patients.[17,44,48] In our sample, most of the patients declared to feel satisfied with their relationship with the partner, and around 85% have a stable couple relationship. However, they declared that the disease affected their sexual life, especially by reducing sexual desire and frequency of sexual intercourses with a statistically significant difference between men and women. One of the reason of reduced sexual intercourse and intimacy could be due to the PD-related sleep disturbances, usually leading to bed separation.[49,50] Moreover, physical changes and dysfunction related to the disease could reduce sexual attraction, decreasing sexual or erotic interests of the partner. Indeed, reduced sexual attractiveness may influence sexual intercourse and any other kind of sexual activities, by affecting both emotional and physical aspects of sexuality. In our sample, men reported to feel less attractive to their partners than women (*P*- < .01) with a worsening of their sexual life, confirming how the psychological aspects may influence sexual function, and how important this issue is for man self-esteem.[50]

Another critical point pertaining to the sexual aspects in PD patients is the effect of disease onset and the dopaminergic drug on sexual functioning. Unexpectedly, we found a negative effect of the dopaminergic therapy on masturbation, sexual activity, and sexual intercourses (reduction of 32.51%). In particular, up to 83% referred an increase in occurrence of sexual problems after the beginning of the drug treatment. On the contrary, about 30% of the patients presented with an increased sexual desire. In fact, although PD patients usually reported impairment in both libido and sexual response, dopamine replacement therapy is often related to impulse control disorders, including hypersexuality and compulsive sexual behavior,[27–29] as dopamine is believed to facilitate sexual arousal. However, increased sexual desire does not always correspond to an achievement of satisfied orgasm owing to concurrent ED.[29]

Sexual unsatisfaction, in addition to the reduction in sexual intercourse, may enhance a perception of negative mood, such as frustration, anxiety, and anger with reduced self-esteem, as in our sample. In fact, all these aspects have a negative influence on the relationship with the partner, with a consequent increase in caregiver burden (as demonstrated by CBI scores). Notably, statistically significant difference in UPDRS-IV, a high sensitive tool to detect motor fluctuation,[51] could have influenced this result ($P = .04$). However, the difference was not present when the differences between patients with and without SD were evaluated ($P = .15$). This issue is more evident in males than females, further supporting the higher importance of sexual intercourse to man's self-esteem. In fact, sexual performance and satisfaction of the partner is an important issue of their self-esteem and sense of masculinity. Buhmann et al reported that orgasmic dysfunction in men with PD was perceived with fear of not gratifying their partners and avoidance of sexual activities. Then, the reaction to SD could be so severe as to compromise the patients' relationship, especially with their partner, often contributing to variation in sexual intercourse, reduction of sexual desire, worsening of depression symptoms, and withdrawal from their relationship.[18,52]

Although the patients reported a satisfying relationship with the partner, about half of them believed that their relationship had changed due to their sense of isolation, aggression, and apathy. About 30% of the interviewed caregivers confirmed these changes in patients' behavior after the PD diagnosis. About 29% were unsatisfied or very unsatisfied about their quality of life, and this is in our opinion a low percentage if we consider age and age-related diseases of our patients, which lived in 3 different regions of Italy. Indeed, the geographical area, the related sociodemographic and economic features may affect quality of life, as well as patient's attitude toward sexuality. This is the reason why we have carried out our study in 3 centers located in different areas of our country (ie, island, southern and northern Italy) reducing the bias related to the sociodemographic features of the sample, better extending our results to the Italian PD population.

With regard to depression, our findings showed that women were more affected by mood alterations than men (21.1% vs 14.2%), showing a higher prevalence of female patients in treatment with anxiolytics/antipsychotics (in our sample, about one third of the patients were treated with such drugs).

Antidepressants are known to impair sexual function, mainly leading to orgasmic disorders,[50] and this iatrogenic cause should be taken into account. Unfortunately, we have not evaluated the impact of antidepressants on sexual function, as we were unaware about the exact time the patients started the drugs. Kotková et al[53] identified sadness as the strongest factor influencing sexual health in men and depression and anxiety as the main factors in women. Indeed, depression or anxiety in PD may reduce libido and orgasmic ability,[53–55] as demonstrated in our sample.

Moreover, we have to underline that sexual issue is still an embarrassing topic for women. In fact, in our sample, about 40% of female did not declare the type of SD compared to 6% of men. This issue should move clinicians toward dealing with sexual topics when interviewing their PD patients, also whether they did not spontaneously disclose this.

Although older age is a recognized risk factor for the development of SD in men, recent literature reported that SD was more frequent in early-onset than late-onset PD patients.[56,57] This issue supports the idea that SD in PD is related more to the disease than aging itself.

However, according to some literature data,[15,19,20,40] we have demonstrated that age and depression are important predictors of SD in such a disease.

Statistically significant differences between subjects with SD and subjects without SD with regard to UPDRS-I-III and HAM-D were found, demonstrating how motor impairment and reduction of participation in activities of daily living may affect sexual function, and raising the idea that rehabilitation of motor performance could also improve patient's sexuality.

It is well known that human sexual behavior is a complex process resulting from a balanced functioning of the person's mental, autonomic, sensory, and motor systems and an appropriate function of the neurological, vascular, and endocrine system.[58] Thus, it is clear that any factors involving these systems could negatively affect sexuality.[59,60] A high percentage of comorbidity (up to 75%), especially hypertension, was found in our PD sample without gender differences. In the general population, it has been shown that a higher rate of SD is present in untreated hypertensive men, as compared to normotensive men. Furthermore, antihypertensive drugs, especially in combination therapy, have been related to SD.[61,62] However, we found that only diabetes mellitus was significantly associated with a high prevalence of SD. Diabetes has been strongly associated with SD in both men and women in the general population,[63–65] and it represents a risk factor for SD, with regard to ED, with a prevalence ranging between 27% and 75%.[66,67] A higher prevalence of SD (53.4%)—significantly higher in menopause, 63.9%—was reported in diabetic women, as compared to the general population.[67] Then, we can postulate that hypertension, diabetes mellitus, and other comorbidities may worsen SD in PD, but this issue should be demonstrated in larger multicenter studies.

Our study has some limitations. The cross-sectional design of the study may represent a principal limitation because of information based on data gathered for a specific point in time. However, we also choose to select a semi-structured interview to integrate and enhance clinical information. This kind of interview is well suited for the exploration of the perceptions and opinions of respondents regarding complex and sometimes sensitive issues, as SD is. Our semi-structured interview has already been used in previous studies investigating either SD induced by intrathecal baclofen[41] or associated to multiple sclerosis.[68,69] Moreover, our interview is in line with the tool used by Buhmann et al in their study of quality of sexual life in patients with PD, as we have assessed SD in different periods, allowing a quasi-longitudinal description of sexual symptoms and behavior as in a one-point cross-sectional investigation.

The sample could be not large enough to correctly generalize the real PD prevalence in this patients' population. However, the multicenter design involving 3 different geographical areas may somehow extend the results to a typical PD Italian population.

The IIEF/FSFI used to investigate SD assesses the relationship with a current partner in the 4 weeks before the evaluation, only providing a superficial characterization of non–sexually active patients. This could lead to either overestimate or underestimate SD prevalence in elderly neurological patients. This is the reason why we developed a semi-structured questionnaire to better investigate the main sexual concerns of PD patients, taking into account disease- and drug-related SD,[41,69,70] although recall bias should be taken into consideration.

The evaluation of the sexual body image would be a crucial contribution in understanding changes of sexual intercourse and sexual desire. Indeed, it has been shown that frontal-lobe dysfunctions in PD patients are associated with lack of motivation and self-initiation, which may account for a reduction in sexual interest with consequent SD.[70]

The lack of a control group is another important limit, although there are growing data on SD in the general elderly population,[71] as well as regarding the difference in SD prevalence between PD patients and healthy controls.[72] Then, according to literature data, our study confirms a high prevalence of SD in patients, especially in males with PD.

Finally, our study lacks endocrinological assessment because it was carried out on outpatients and it was not possible to clarify the relationship between sexual hormones, especially testosterone levels, and the pathogenesis of SD in PD.[73–75] However, some data concerning the organic versus psychogenic SD origin may derive from the DIQ tool we used.

In conclusion, SD is a highly prevalent and devastating problem in patients affected by PD, negatively affecting their quality of life. We underlined how gender difference may affect SD, as well as the role of other important variables, including depression, the type of relationship, and comorbidities, in causing the dysfunction. Clinicians dealing with neurological disorders should pay more attention to sexual issues, also in women, as discussing and treating sexual problems enters the framework of a holistic approach, which is mandatory in chronic illness, including PD. Further prospective case-control longitudinal studies should be fostered to confirm our findings and better manage this overlooked problem.

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