Investigation of Urination Disorder in Parkinson's Disease

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Abstract

Background: Urination disorders are common in Parkinson's disease (PD) and respond poorly to medication. This study aimed to analyze the risk factors for urination disorders in PD.

Methods: Ninety-one patients with PD (aged 34–83 years old) were recruited. Patients were assessed with the Unified PD Rating Scale (UPDRS), Hoehn and Yahr stage, Pittsburgh Sleep Quality Index (PSQI), Hamilton Depression Rating Scale (HAMD), and Hamilton Anxiety Scale (HAMA). Micturition number was recorded, and Type B ultrasound was used to evaluate residual urine. Statistics was performed using binary logistic regression, bivariate correlations, and Chi-square and *t*-tests.

Results: Of 91 patients, urinary dysfunction occurred in 55.0%. Among these, 49.5% suffered with nocturia, 47.3% with pollakiuria. Nocturia number had a positive linear relationship with HAMA score (odds ratio [OR] = 0.340, P = 0.001), HAMD score (OR = 0.323, P = 0.002), duration of L-dopa medication (OR = 0.328, P = 0.001), dose of L-dopa (OR = 0.273, P = 0.009), UPDRS-II (OR = 0.402, P = 0.000), UPDRS-III score (OR = 0.291, P = 0.005), and PSQI score (OR = 0.249, P = 0.017). Micturition number over 24 h was positively associated with HAMA (OR = 0.303, P = 0.004) and UPDRS-II scores (OR = 0.306, P = 0.003). Of patients with residual urine, 79.3% had a volume of residual urine <50 ml. Residual urine was present in 44.4% of the patients with nocturia, 46.5% of the patients with pollakiuria, and 80.0% of the patients with dysuria. More men than women had residual urine (35.2% male vs. 13.3% female; P = 0.002).

Conclusions: Nocturia and pollakiuria were common micturition symptoms in our participants with PD. Nocturia was associated with depression, anxiety, sleep problems, and severity of PD. Pollakiuria was associated with anxiety and severity of PD. Male patients were more prone to residual urine and pollakiuria.

Key words: Nocturia; Parkinson's Disease; Risk Factors; Urine Disorders

INTRODUCTION

Urinary dysfunction frequently occurs in patients with Parkinson's disease (PD) with a reported prevalence of 38–71%.^[1,2] It can be observed at any stage of the disease,^[3] and responds poorly to medication.^[4,5] Two main types of urinary dysfunction are storage and voiding symptoms. Storage symptoms include nocturia, pollakiuria, urgency, and incontinence. Voiding symptoms include dysuria and prolonged time of micturition. It has been difficult to evaluate the extent to which patients with PD are affected by urinary dysfunction because prostatic hyperplasia, aging, and sleeping disorders can also influence micturition. Three-quarters of healthy individuals consider that the most common reason for micturition during the night is insomnia.^[6,7]

Urination is a complicated process; nerve transmission controlling this process may include the central autonomic

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network, spinal cord, and peripheral sympathetic and parasympathetic ganglions.^[3,8] The mechanisms leading to urinary dysfunction in patients with PD are still unclear. Functional imaging has revealed activation in the putamen in PD patients with a full bladder, whereas in healthy individuals activation is seen in the globus pallidus.^[9,10] Investigations of risk factors may provide clues but have not been explored satisfactorily in previous research.

Here, we analyze clinical factors those may affect micturition in patients with PD, including age, age of onset, gender,

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Received: 09-04-2015 **Edited by:** Yuan-Yuan Ji **How to cite this article:** Zhang LM, Zhang XP. Investigation of Urination Disorder in Parkinson's disease. Chin Med J 2015;128:2906-12. course of disease, sleep, disease severity, anti-PD agents, depression, and anxiety. We aimed to define risk factors for urinary dysfunction in PD.

Methods

Study design

This study was a prospective, case-record, and patient-centered study. Ninety-one patients, aged 34-83 years (mean age: 68.3 ± 8.9 years), were recruited from September 2011 to June 2014. They all had a primary diagnosis of PD according to UK PD Society Brain Bank criteria. Of these, 61 were male and 30 were female. Patients received between 150 and 1500 mg/d of L-dopa and had taken this medication for between 0.5 and 9 years. For patients who did not take L-dopa, the dose and duration was designated as "0". Other medications taken by some patients included benzhexol hydrochloride (2-7 mg/d) and pramipexole (0.375-2.250 mg/d), which was taken as a single-agent therapy or in combination with L-dopa. Patients were assessed using the Unified PD Rating Scale (UPDRS), Hoehn and Yahr (H and Y) at "on stage" (where motor symptoms were improved to maximize outcomes), Pittsburgh Sleep Quality Index (PSQI), Hamilton Depression Rating Scale (HAMD, 24 items), and Hamilton Anxiety Scale (HAMA).

Nocturia was defined as micturition more than twice a night after falling asleep. Pollakiuria was defined as micturition more than 8 times over 24 h. Type B ultrasound (GE Voluson E8, USA) was used to evaluate residual urine and exclude prostate disease. Exclusion criteria were drinking large amounts of water, urinary infection, diabetes insipidus and diabetes mellitus, and cognitive function impairment assessed using the Montreal Cognitive Assessment Scale.

The study was approved by the Local Ethical Committee of Harbin Medical University, and all patients signed written informed consent.

Statistical analysis

Values were expressed as *n* or mean \pm standard deviation (SD). Potential risk factors for nocturia, pollakiuria, and residual urine were analyzed using binary logistic regression. Bivariate correlations were used to analyze risk factors for nocturia and micturition number. The Chi-squared test was used to evaluate residual urine in patients with or without nocturia, pollakiuria, and dysuria. *T*-tests were used to compare age between male and female patients, as well as to compare the average volume of residual urine between male and female patients. All statistics were performed using PASW Statistics18.0 (SPSS Inc., Chicago, IL, USA). A *P* < 0.05 was considered as statistically significant.

RESULTS

Clinical data

In the 91 patients recruited, age ranged from 34 to 83 years old (<60 years: 12.1%; 60–70 years: 37.4%; 71–80 years: 47.3%; >80 years: 3.3%). There were 61 (67.0%) male patients with a mean age of 67.3 ± 9.4 years and 30 (33.0%) female patients with a mean age of 70.4 ± 7.6 years. Male and female patients did not

differ significantly in age (t = -1.587, P = 0.116). Thirty-eight patients had mood symptoms (41.8%), including 28 cases with depression (28.6%) and 27 cases with anxiety (29.7%). Comorbid depression and anxiety was seen in 16 cases (17.6%). The course of disease ranged from 0.5 to 17 years with 42 cases (46.2%) having a course of <5 years, 38 cases (41.8%) having a course of 5–10 years, and 11 cases (12.1%) having a course longer than 10 years. Seventy cases had an H and Y grade of 1–2.5 (76.9%) and the other 21 had an H and Y grade of 3–5.

Distribution of urinary dysfunctions

Urinary dysfunction was reported in 50 patients with PD (55.0%). Among the 91 participants, 45 suffered with nocturia (49.5%), 43 with pollakiuria (47.3%), 10 with urgent micturition (11.0%), 3 with urinary incontinence (3.3%), and 10 with dysuria (11.0%). Among the 43 patients with pollakiuria, 38 cases had nocturia simultaneously. All patients with dysuria were male, of which 8 had nocturia and 7 had pollakiuria.

Relationship between clinical characteristics and nocturia

Statistical results suggest that UPDRS-II score was higher in patients with nocturia than those without nocturia (P = 0.003). Patients with nocturia slept for shorter periods (P = 0.038) and had larger dosages of L-dopa (P = 0.012). There was no significant difference between patients with or without nocturia in scores for HAMA, HAMD, H and Y, PSQI, or UPDRS-III. There were also no significant differences in age, age of onset, course of disease, gender, dopamine receptor agonist medication, benzhexol hydrochloride medication, end of dose, or dysuria rate [Table 1].

Nocturia number was defined as the number of occasions of micturition during the night. Analysis showed that nocturia number had a positive linear relationship with HAMA score (odds ratio [OR] = 0.340, P = 0.001) [Figure 1a], HAMD (OR = 0.323, P = 0.002) [Figure 1b], PSQI (OR = 0.249, P = 0.017) [Figure 1c], L-dopa dose (OR = 0.273, P = 0.009) [Figure 1d], duration of L-dopa medication (OR = 0.328, P = 0.001) [Figure 1e], UPDRS-II (OR = 0.402, P = 0.000) [Figure 1f], and UPDRS-III (OR = 0.291, P = 0.005) [Figure 1g]. Nocturia number was not related to the course of disease (OR = 0.183, P = 0.083), age (OR = 0.156, P = 0.140), or sleeping time (OR = -0.176, P = 0.095).

Risk factors for pollakiuria

Compared with patients without pollakiuria, patients with pollakiuria had higher HAMA and UPDRS-II scores. More patients with pollakiuria were medicated with pramipexole and male (P < 0.05). There were no significant differences between patients with and without pollakiuria on HAMD score, age, age of onset, course of disease, actual sleeping time, PSQI score, dose and duration of L-dopa medication, H and Y stage, UPDRS-III score, or benzhexol medication [Table 2].

Micturition number over 24 h had a positive linear correlation with HAMA score (OR = 0.303, P = 0.004) [Figure 1h]

Items	No nocturia ($n = 46$)	Nocturia ($n = 45$)	Р	OR (95% CI)
HAMA	8.9 ± 6.6	12.2 ± 8.6	0.276	1.061 (0.954-1.180)
HAMD	12.9 ± 7.5	16.2 ± 8.9	0.439	0.966 (0.885-1.055)
Age (years)	67.6 ± 10.2	69.0 ± 7.4	0.248	1.450 (0.772-2.724)
Onset age (years)	63.1 ± 10.7	62.9 ± 7.9	0.275	0.705 (0.376-1.322)
Course of disease (years)	4.7 ± 3.4	6.1 ± 2.9	0.302	0.703 (0.360-1.372)
Sleeping time (hours)	6.5 ± 2.0	5.8 ± 1.4	0.038	0.688 (0.483-0.980)
PSQI	6.4 ± 6.3	8.8 ± 6.5	0.361	0.939 (0.820-1.075)
Dose of L-dopa (mg/d)	344.6 ± 241.0	508.6 ± 291.5	0.012	1.004 (1.001-1.007)
H and Y stage	2.2 ± 0.8	2.5 ± 0.7	0.226	0.442 (0.118-1.659)
UPDRS-II	12.1 ± 5.7	16.1 ± 6.5	0.003	1.333 (1.100–1.615)
UPDRS-III	26.7 ± 10.7	31.3 ± 11.2	0.149	0.938 (0.860-1.023)
End of dose (yes/no)	14/32	24/21	0.534	1.600 (0.364-7.046)
Male/female	27/19	34/11	0.063	3.128 (0.939-10.417)
DA agonist (use/no)	9/37	8/37	0.130	0.294 (0.060-1.432)
Artane (use/no)	2/44	5/40	0.081	0.169 (0.023-1.246)
Dysuria (yes/no)	3/43	7/38	0.442	2.292 (0.277-18.963)

Binary logistic regression was used, numeration data are expressed as numbers and measurement data are expressed as mean \pm SD. *CI*: Confidence interval; *OR*: Odds ratio; HAMA: Hamilton Anxiety Scale; HAMD: Hamilton Depression Rating Scale; UPDRS: Unified PD Rating Scale; H and Y: Hoehn and Yahr stage; PSQI: Pittsburgh Sleep Quality Index; DA agonist: Dopamine receptor agonist; SD: Standard deviation; L-dopa: Levodopa; PD: Parkinson's disease.

Items	Without pollakiuria ($n = 46$)	With pollakiuria ($n = 45$)	Р	OR (95% CI)
HAMA	8.4 ± 6.6	12.9 ± 8.5	0.011	1.155 (1.033–1.292)
HAMD	13.1 ± 7.8	16.0 ± 8.8	0.599	0.975 (0.888-1.071)
Age (years)	67.4 ± 10.2	69.4 ± 7.2	0.884	1.041 (0.610–1.774)
Onset age (years)	62.5 ± 10.4	62.9 ± 7.9	0.903	1.034 (0.609–1.753)
Course of disease (years)	5.0 ± 3.4	5.9 ± 3.1	0.686	1.122 (0.642-1.960)
Sleeping time (hours)	6.3 ± 2.0	6.0 ± 1.5	0.325	0.837 (0.588-1.193)
PSQI score	6.5 ± 6.2	8.8 ± 6.6	0.272	0.925 (0.805-1.063)
Dose of L-dopa (mg/d)	389.6 ± 242.6	466.0 ± 311.2	0.141	1.002 (0.999-1.005)
UPDRS-II	12.4 ± 5.8	15.9 ± 6.7	0.007	1.305 (1.077–1.583)
UPDRS-III	27.5 ± 10.8	30.6 ± 11.5	0.221	0.946 (0.865-1.034)
End of dose (yes/no)	18/30	20/23	0.254	2.471 (0.522-11.686)
Male/female	28/20	33/10	0.045	3.576 (1.030-12.414)
DA agonist (use/no)	8/40	9/34	0.012	0.118 (0.022-0.620)
Artane (use/no)	2/46	5/38	0.110	0.202 (0.029–1.433)
Dysuria (yes/no)	3/45	7/36	0.681	0.639 (0.075-5.420)
H and Y stage	2.3 ± 0.8	2.4 ± 0.7	0.032	0.228 (0.059-0.881)

Data were analyzed using binary logistic regression. Numeration data are expressed as numbers and measurement data are expressed as mean \pm SD. *OR*: Odds ratio; *CI*: Confidence interval; PD: Parkinson's disease; HAMA: Hamilton Anxiety Scale; HAMD: Hamilton Depression Rating Scale; UPDRS: Unified PD Rating Scale; H and Y: Hoehn and Yahr stage; PSQI: Pittsburgh Sleep Quality Index; DA agonist: Dopamine receptor agonist; L-dopa: Levodopa; SD: Standard deviation.

and UPDRS-II score (OR = 0.306, P = 0.003) [Figure 1i]. It was not related with HAMD score (OR = 0.155, P = 0.143), course of PD (OR = 0.191, P = 0.070), age (OR = 0.123, P = 0.244), sleeping time (OR = -0.160, P = 0.129), PSQI score (OR = 0.187, P = 0.076), duration of L-dopa medication (OR = 0.217, P = 0.039), dose of L-dopa (OR = 0.139, P = 0.189), or UPDRS-III (OR = 0.155, P = 0.144).

Risk factors for residual urine

Of all patients, 29 (31.9%) had residual urine with a residual urine volume of <50 ml in 23 cases (79.3%), 50–100 ml in 2 cases (6.9%), and more than 100 ml in

4 cases (13.8%). Residual urine was detected in 44.4% of the patients with nocturia and 19.6% of the patients without nocturia. It was detected in 46.5% of the cases with pollakiuria and 18.8% of the cases without pollakiuria. It was also detected in 80% of the cases with dysuria and 25.9% of the cases without dysuria. The average volume of residual urine was 153.5 ± 248.5 ml in patients with dysuria and 8.7 ± 19.8 ml in patients without dysuria (t = -5.287, P = 0.000).

Residual urine was detected in more male than female patients (P = 0.002). Patients with residual urine also had higher HAMA scores, higher UPDRS-II scores, and more

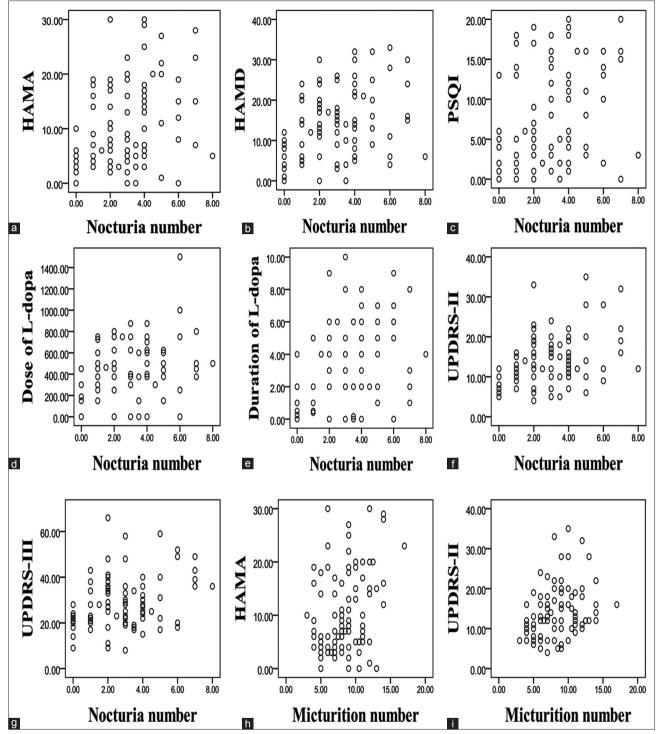


Figure 1: Linear relationship between nocturia and micturition number with risk factors. (a-g) Reflect positive linear relationships between nocturia number and risk factors; (h and i) Positive linear relationships between micturition number and Hamilton Anxiety Scale (HAMA) and Unified Parkinson's Disease Rating Scale (UPDRS)-II scores.

often had wearing-off phenomenon (in which symptom improvements gained from L-dopa do not last until the next dose) [Table 3]. There were no statistical differences between patients with and without residual urine in HAMD scores, age, age of onset, course of disease, PSQI score, pramipexole, artane and L-dopa medication, duration of wearing-off, H and Y stage, or UPDRS-III score.

DISCUSSION

In our study, nocturia was most common, present in 49.5% of the patients with PD, followed by pollakiuria, urgent micturition, dysuria, and urinary incontinence. Urination dysfunction appears to occur in the early stages of PD because most patients (76.9%) were in the 2–2.5 H and Y stage with a disease duration of <5 years. Our results are

Items	No residual urine ($n = 62$)	With residual urine $(n = 29)$	Р	OR (95% CI)
НАМА	8.9 ± 7.2	14.7 ± 8.0	0.023	1.173 (1.022–1.345)
HAMD	12.7 ± 7.6	18.3 ± 8.8	0.659	1.025 (0.917-1.146)
Age (years)	67.5 ± 9.9	70.1 ± 7.4	0.421	1.620 (0.500-5.246)
Male/female	36/26	25/4	0.002	33.846 (3.554–322.323)
Onset age (years)	63.1 ± 9.9	62.9 ± 6.3	0.524	0.681 (0.209-2.217)
Course of disease (years)	4.6 ± 2.7	7.1 ± 3.8	0.690	0.773 (0.218-2.739)
PSQI	6.7 ± 6.1	9.5 ± 6.8	0.212	0.886 (0.733-1.071)
DA agonist (use/no)	9/53	5/24	0.063	0.127 (0.014-1.116)
Artane (use/no)	4/58	3/26	0.340	0.342 (0.038-3.101)
Dose of L-dopa (mg/d)	372.8 ± 237.5	538.8 ± 326.3	0.049	1.004 (1.000-1.009)
H and Y stage	2.2 ± 0.6	2.8 ± 0.9	0.990	1.011 (0.181-5.656)
UPDRS-II	12.0 ± 4.7	18.5 ± 7.4	0.017	1.372 (1.058-1.680)
UPDRS-III	26.4 ± 9.4	34.5 ± 12.7	0.102	0.895 (0.783-1.022)
End of dose (yes/no)	21/41	17/12	0.042	9.029 (1.080-75.494)
Duration of wearing-off (years)	0.7 ± 1.4	2.0 ± 2.1	0.083	1.481 (0.950-2.310)

Data were analyzed with binary logistic regression. Numeration data are expressed as numbers and measurement data are expressed as mean \pm SD. *OR*: Odds ratio; *CI*: Confidence interval; HAMA: Hamilton Anxiety Scale; HAMD: Hamilton Depression Rating Scale; UPDRS: Unified PD Rating Scale; H and Y: Hoehn and Yahr stage; PSQI: Pittsburgh Sleep Quality Index; L-dopa: Levodopa; SD: Standard deviation; PD: Parkinson's disease.

consistent with previous reports in which the prevalence of storage and voiding symptoms in PD were 35–83% and 17–27%, respectively.^[11-13] However, studies have reported different prevalence rates of urination disorders in early and advanced PD.^[14,15] There were few patients at an advanced stage of disease in our study. Therefore, recruitment of more patients including those at an advanced stage of PD may provide more accurate data.

The mechanism of nocturia in patients with PD remains unclear. It has been suggested that urination disorders in PD may be related to lesions in sympathetic and parasympathetic nerves,^[16] Barrington's nucleus in the pons, locus ceruleus, periaqueductal grav matter, frontal lobe, and the basal ganglia.^[17,18] Such an array of lesions complicates the clinical picture of urination disorders. In this study, UPDRS-II scores were higher in patients with nocturia (P < 0.05), and nocturia number was positively correlated with UPDRS-II and UPDRS-III scores. This suggests that nocturia is related to the severity of PD. This is consistent with reports elsewhere, with bladder function and severity of urination disorders deteriorating as PD develops.^[13,15,19] This may be due to altered frontal-basal ganglia dopaminergic circuits, which results from dopaminergic neuron degeneration in PD.^[20,21] This may lead to a decrease in the suppression of micturition reflexes by this circuit.

It is uncertain whether L-dopa medication can improve micturition disorders. Some have reported that L-dopa improves micturition symptoms, but others have reported conflicting results.^[12,22,23] In addition, the effects of L-dopa on bladder function are unknown.^[20,24,25] In this study, the dose of L-dopa was higher in patients with nocturia than without nocturia (P = 0.012). Nocturia number also showed a positive linear correlation with L-dopa dose (OR = 0.328, P = 0.001). These data suggest that taking L-dopa may increase the risk of nocturia. It is possible that in the early

stages of PD, dopaminergic neurons are not exhausted, and certain numbers of dopaminergic synapses are still preserved. As such, ectogenic L-dopa can be converted to dopamine in dopaminergic neurons in the frontal-basal ganglia dopaminergic circuit, allowing it to remain functional. However, with the further development of PD, there is significant loss of dopaminergic neurons. At this stage, ectogenic L-dopa is metabolized to dopamine at nondopaminergic neurons, and dopaminergic synapses are not effectively activated in the frontal-basal ganglia dopaminergic circuit. This may affect the micturition reflex, leading to the differences in micturition disorders associated with L-dopa treatment.

A sense of the bladder filling can lead to urination during the night and affect sleeping time and quality. Our results suggest that PSQI score was higher in patients with nocturia (indicating worse quality sleep), and actual sleeping time was an hour longer in patients with nocturia than without nocturia (P = 0.038). In addition, nocturia number appeared to be positively associated with PSQI score. This seems to suggest that urination dysfunction contributed to sleeping quality, but we were not able to demonstrate a cause and effect relationship the two. Nocturia number was also associated with depression and anxiety. However, this association was not replicated in the binary logistic regression [Table 1], which may be because we included many covariates in the statistical analysis. In this study, there was no correlation of nocturia with age, age of onset, gender, course of disease, H and Y stage, wearing-off, antiparkinsonian medication, or dysuria.

Detrusor hyperactivity or overactive bladder syndrome has been cited as the main reason for urination disorders in patients with PD. Urodynamic tests have shown that 45–93% of patients with PD suffer from detrusor hyperactivity.^[13,19] In addition, pollakiuria was found to indicate detrusor hyperactivity.^[7] In our study, pollakiuria occurred in 47.3% of the PD patients and was associated with HAMA, UPDRS-II, and H and Y stage. Micturition number over 24 h was also positively correlated with HAMA and UPDRS-II scores. This suggests that pollakiuria is related to the severity of disease and mental state, which is consistent with a previous report.^[26]

Residual urine volume is the only urodynamic parameter reported to be related to the severity of PD. In this study, 31.9% of the patients had residual urine with a residual urine volume of <50 ml in most cases. Patients with residual urine were prone to both nocturia and pollakiuria. Previous reports have shown an average residual urine volume of 34 ml in patients with PD and only a small proportion (around 6%) had a residual urine volume of more than 100 ml.^[27] Such results support the hypothesis that increased residual urine volume may be due to detrusor hypofunction or incoordination of detrusor and sphincter.^[19] This was also demonstrated in our results, in which most patients with dysuria had residual urine and their residual urine volume was more than that of patients without dysuria.

A finding in our study not previously reported elsewhere is the higher number of male patients (41.0%) with residual urine than female (3.3%). In addition, more men showed pollakiuria. This is even though dysuria caused by prostatic hyperplasia had been ruled out through ultrasonography examination. It was previously reported that men are prone to urination disorders while women are more prone to weight loss or sweating disorder,^[28] but the reasons for these differences remain unclear. The antiparkinsonian medication artane affects bladder function, but in this study, we did not find any relationship between artane medication and residual urine. However, there were few patients using artane, and so the small sample size may have lacked power to show any relationship present. Residual urine was not related to age, age of onset, course of disease, PSQI score, pramipexole and L-dopa medication, anxiety, UPDRS-II, or wearing-off. It has been reported that residual urine is related to dyskinesia of the lower body and gait disorder in patients with PD^[29] but that was not replicated in this study.

In conclusion, our study suggests that urination disorders are common in patients with PD. Nocturia was the most common symptom, followed by pollakiuria. Nocturia number was positively associated with depression, anxiety, sleeping quality, and severity of PD, whereas pollakiuria was associated with anxiety and severity of PD. Our results suggest that urination disorders in PD are associated with various risk factors, including both PD and non-PD related factors. Treatment should be provided according to individual circumstances, taking these factors into account. Although we found here that male patients were more prone to residual urine and pollakiuria, it is unclear why that should be. As such, future research should investigate the mechanisms leading to greater risk for male patients.

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Conflicts of interest

There are no conflicts of interest.

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