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Original Articles

Nocturnal polyuria is common in Parkinson's and is associated with orthostatic hypotension

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ABSTRACT

Background: Nocturia is the most common lower urinary tract symptom (LUTS) in Parkinson's disease (PD) and impacts sleep and subsequent daytime function. Often nocturia in PD is attributed to overactive bladder, however we explored the contribution of the over-production of urine at night, nocturnal polyuria (NP), as another factor.

Objectives: To assess the prevalence and severity of NP in a PD cohort with LUTS and explore associations with autonomic and other patient characteristics.

Methods: Sub-study nested within a trial for LUTS in PD. All participants performed 72-hour bladder diaries. Nocturnal polyuria index (NPi) was calculated from diaries and key associations were explored.

Results: 62.6 % of participants had NP based on the NPi33 threshold (producing > 33 % urine at night). Increasing NPi was strongly significantly associated with greater nocturia (OR 1.7 per 5 % NPi unit; 1.5–2.0; $P < 0.001$). A significant association was observed between NPi and orthostatic hypotension (OR 1.2 per 5 % NPi unit increase; 1.0–1.4; $P = 0.03$) and reported cardiovascular symptoms (coefficient 0.07; 0.03–0.11; $P = 0.002$). A marked association was seen with severe NP and orthostatic hypotension (OR 4.9; 1.56–15.57; $P = 0.006$).

Conclusion: NP is very common in this PD cohort symptomatic for LUTS, and is closely associated with increasing rate of nocturia. NP is linked to cardiovascular symptoms and autonomic dysfunction, particularly blood pressure lability which may be causal or simply reflect advanced disease state.

1. Introduction

Lower urinary tract symptoms (LUTS) are common in Parkinson's disease (PD), with nocturia being the most frequently reported, present in an estimated 59 % of patients [1]. Nocturia can be the result of numerous processes, including urological and non-urological causes and is frequently multifactorial [2], for example due to impaired storage due to overactive bladder, or through the consequences of fluid overload or obstructive sleep apnoea. Nocturia leads to sleep deprivation, subsequently causing fatigue and potentially deleterious effects on cognition and function during the day. Nocturia also necessitates patients getting up at night when in the "off" motoric state, potentially increasing the risk of falls and injury. For these reasons, nocturia is an important multifaceted symptom which is often overlooked, but requires proactive management.

LUTS in PD have typically been thought to arise from overactive bladder (OAB), a syndrome of impaired physiological control of the urine storage, leading to symptoms such as urgency and urgency incontinence as well as nocturia [3]. Nocturnal polyuria (NP) is another cause of nocturia that is well-recognised in general populations as a cause of nocturia [2,4]. Rather than affecting ability to store normal volumes of urine as seen in OAB, nocturnal polyuria is the over production of urine at night relative to the day, causing the patient to wake to void this excess. NP has been described in PD in three previous small studies [5,6], as well being assessed as an outcome measure in two interventional studies [5–7]. The effect of NP is important to delineate, as the cause of this is likely to be renal or systemic, rather than primary bladder dysfunction as in OAB. Elucidating the role of these phenomena

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will improve our understanding of the pathological processes in PD and facilitate the development of new treatments, alongside directing the management of symptoms on an individual basis.

This study aimed to assess the prevalence of NP in a cohort symptomatic for LUTS. In addition it explored associations between NP and other patient phenotypic features such as the extent of nocturia episodes and the link to associated autonomic symptoms.

2. Methods

2.1. Study design

This was a cross-sectional study nested within the STRIPE (Stimulation of the Tibial nerve Repetitively in improve Incontinence in Parkinson's Electronically) randomised control trial of neuromodulation for LUTS in PD (ISRCTN 1148495). STRIPE was approved by the Camden and Kings Cross Research Ethics Committee in June 2021, with the NP sub-study explicitly designed in from the start. Enrolment for STRIPE ran between October 2021 and July 2023 and all participants taking part in the main study were included in the NP sub-study. Data was taken only from baseline assessment to prevent any potential interference from trial procedures impacting the results.

2.2. Participants

The methodology of STRIPE has been described elsewhere [8]. In brief, key inclusion criteria were a diagnosis of idiopathic PD (as determined by their own Parkinson's specialist) and clinical symptoms suggestive of OAB, based on a history of urinary urgency during telephone interview. Participants were excluded if they had an implanted electronic device (pacemaker, deep brain stimulator); previous sacral neuromodulation, tibial nerve stimulation or intra-detrusor botulinum toxin injections in the past year; cognitive impairment to the extent of being unable to engage in assessments or provide informed consent; abnormality of both lower limbs precluding device placement; deep vein thrombosis in past three months, history of severe benign prostatic hypertrophy; proven significant post-void residual and current treatment for urological cancer.

Potential participants for STRIPE were recruited by clinician referral, through screening of participants of the PRIME-UK cross-sectional trial undertaken by our team, and via advertising through the charity Parkinson's UK. The PRIME cross-sectional study was an observational study of people with parkinsonism living in the catchment area of Royal United Hospital Bath NHS Foundation Trust [9]. Participants completed questionnaire booklets which included the International Consultation on Incontinence Questionnaire – male/female Lower Urinary Tract Symptoms (ICIQ mLUTS and fLUTS) questionnaires, used to ascertain which participants were symptomatic for LUTS. Suitable PRIME-UK participants who had consented to be contacted about other studies were sent details for STRIPE. Participants enrolling in STRIPE attended from across the United Kingdom, visiting the study site located at the Research Institute for Care of the Older Person (RICE).

Although enrolment in the main STRIPE study was dependent on a clinical picture of OAB, potential participants who reported nocturia alone could take part after undertaking an eligibility diary to screen for severe NP. Where severe NP was not present, the potential participant could proceed to enrol in STRIPE. Individuals undertaking this eligibility process who were unable to proceed to the main STRIPE study were included in the NP sub-study, as well as potential participants who attended for an enrolment session but were unable to take part in the subsequent intervention (significant post-void residual, inability to use trial device). Permission was sought from these ineligible potential STRIPE participants for their data to be included in the sub-study.

2.3. Data collection

Data on demographic details, duration of PD and a medication history were collected as part of the STRIPE enrolment process. All potential STRIPE participants verbally consented to undertake a 72-hour bladder diary before attending enrolment, or as a screening procedure before booking an enrolment session. Diaries were either collected in person (enrolment) or were sent via post (screening). A bespoke bladder diary was utilised (example in Supplementary Fig. 1). Participants were provided with a measuring jug to measure voided volumes, alongside recording fluid intake. Participants were asked to ensure fluid intake reflected their usual intake patterns and were recorded throughout the period. Where pads were worn, participants were asked to weigh pads and summarise day and night volumes assuming each 1 g increase over dry pad weight indicated 1 ml of urinary incontinence [10]. Where relevant, participants were asked to weigh each pad on their usual time of changing this.

Participants enrolling in STRIPE completed ICIQ mLUTS/fLUTS [11,12] which assesses general LUTS profile with severity categories as well as perceived bother for each item using a 0–10 scale, across 13 questions for men and 12 for women. Participants also completed the scale for Outcomes in Parkinson's disease – Autonomic Dysfunction (SCOPA-AUT) tool [13], the Overactive bladder quality of life tool (OABqol) [14], and underwent the Unified Parkinson's Disease Rating Scale (UPDRS) assessment [15], postural blood pressure assessment and post-void ultrasound scan of the bladder. Blood pressure was taken resting in a supine position and taken on immediately standing and after standing for three minutes. A definition of a fall of 20 mmHg systolic or 10 mmHg diastolic was used for orthostatic hypotension [16]. A definition of blood pressure $>$ 140 mmHg systolic or 90 mmHg whilst lying was used for supine hypertension [17].

2.4. Nocturnal polyuria metrics

The nocturnal polyuria index (NPi) metric of NP was used for the study [18]. This is the most widely used definition. NPi was calculated by dividing the total volume of night-time urine production (including the first void on waking, excluding the last void before bed) by the total urine production over the 24-hour period. This was multiplied by 100 and presented as a percentage. Analysis was carried out on mean NPi values (the mean NPi across the three days of the diary), however maximum NPi was also established (the highest NPi achieved on any given day of the diary).

For NPi, a number of thresholds exist in the literature. NPi33 (NPi $>$ 33 %) is the most commonly accepted cut off for individuals over 65 [19]. NPi50 (NPi $>$ 50 %) was used as a threshold for severe NP, where more than half of 24-hour urine volume is produced during the period of sleep. Furthermore, we defined NPi40 (NPI $>$ 40 %) as moderate NP.

The period from intentionally laying down to sleep at night until rising in the morning to begin the day was taken as the night period for each participant. The number of nocturia episodes used for analysis included the total observed in diaries and self-reported values from ICIQ mLUTS/fLUTS.

2.5. Statistical analysis

Data was stored on a Redcap database (Vanderbilt University, USA) and statistical analysis undertaken using Stata version 17 (Stata Corp LLC, USA). Descriptive data was presented using mean and median values dependent on distribution. Outcome variables were $\log_e$ transformed where positively skewed. A sample size calculation was carried out for the main STRIPE study, but not specifically for this observational sub-study.

We re-parameterised some of our exposures for ease of coefficient interpretation in our regression models; NPi values were fitted into 5 % bands and fluid intake into 100 ml bands, in order to provide more easy

to interpret effect estimates for a moderate unit change. Mean NP values representing the average over 3-day diaries were used where any associations were examined.

We used a variety of different statistical models depending on whether the outcomes were continuous (linear), ordinal (ordinal logistic) or dichotomous (logistic). We firstly examined associations between NPi (exposure) and number of nocturia episodes (outcome) using an ordinal logistic regression model (categories 0–4+). The association between bother (outcome) and NPi (exposure) was performed using an ordinal logistic regression model. Associations between baseline patient characteristics, symptom profile from ICIQ mLUTS/fLUTS (exposures) and NPi (outcome) were estimated using a linear regression model. The association between overall NPi (exposure) and categorical postural hypotension/supine hypertension (outcome) was undertaken using a logistic regression model. The association between NPi category (exposure) and OH (outcome) was also performed using a logistic regression model. The association between NPi (exposure) and numerical lying blood pressure values or SCOPA-AUT questionnaires (outcome) were assessed using a linear regression model. The assumption of proportional odds (parallel regression) was assessed using a Brant test for each ordinal model and regression assumptions checked for each linear model.

3. Results

3.1. Recruitment and baseline characteristics

177 individuals completed 72-hour bladder diaries, comprising the 148 individuals enrolled in STRIPE (83.6 %) and 29 who completed diaries but did not proceed into the trial (16.4 %). Three participants in STRIPE were unable to correctly complete the bladder diary and therefore these data were excluded from the NP sub-study leaving 174 diaries for analysis. Baseline characteristics of participants and summary values from 72-hour bladder diaries are displayed in Table 1.

Table 1
Baseline characteristics of individuals contributing bladder diaries to study (n = 174). Further clinical details were available for participants enrolled in the STRIPE parent study (n = 145)*Postural blood pressure assessment in n = 136 only. SD = standard deviation, ICIQ mLUTS = International Consultation on Incontinence Questionnaire – male Lower Urinary Tract Score, ICIQ fLUTS = female Lower Urinary Tract Score, SCOPA-AUT = Scale for Outcomes in Parkinson's disease – Autonomic Dysfunction, NPi = nocturnal polyuria index.

Overall bladder diary group (n = 174)				
	Mean	Median	Range	(SD)
Age	70.2	71.0	42–87	(7.4)
Duration of disease	7.2	6.0	1–26	(4.7)
Female	35.6 %	–		
Levodopa equivalent dose (mg)	492.0	450	100–1250	(227)
Anti-hypertensives/diuretics	22.0 %	–		
Obstructive sleep apnoea	4.5 %	–		
Subgroup enrolled in STRIPE study (n = 145)*				
UPDRS part III score	40.4	39.0	9–85	(15.0)
ICIQ mLUTS score (n = 91)	15.1	14.5	5–36	(5.4)
ICIQ fLUTS score (n = 54)	13.5	12	5–25	(5.0)
ICIQ mLUTS/fLUTS nocturia frequency	1.9	2	0–4+	(1.2)
SCOPA-AUT score	19.7	18	4–53	(8.4)
*Orthostatic hypotension**	38.2 %	–		
72-hour bladder diary characteristics (n = 174)				
Number of nocturia episodes	1.8	1.7	0–6.5	(1.2)
Day time volume (ml)	1149	1070	395–3111	(471)
Night time volume (ml)	663	600	108–1853	(326)
24-hour fluid intake (ml)	1786	1640	448–3978	(646)
Hours asleep	7.9	8.0	4.3–10.7	(1.0)
Nocturnal polyuria metrics (n = 174)				
Mean NPi over diary period	36.7	36.6	10.0–64.2	(11.3)
Maximum NPi over diary period	44.6	44.7	10.2–93.1	(13.3)
NPi Intra-subject standard deviation over 72-hours	7.7	7.0	0.2–31.4	(4.7)

3.2. Prevalence of nocturnal polyuria and association with nocturia

Nocturnal polyuria was common across the cohort and overall metrics are displayed in Table 1. The mean NPi over the 72-hour diary was 36.7 %. 109 out of 174 participants (62.6 %) had nocturnal polyuria using the NPi33 definition and 136 out of 174 (78.2 %) based on maximum value observed. For higher NPi severity brackets 42.5 % averaged NPi40 across the diary (60.3 % for maximum values) and 12.6 % averaged NPi50 (32.8 % for maximum values).

The association between NPi and frequency of nocturia is demonstrated in the box-whisker plots shown in Fig. 1. A marked increase in the frequency of nocturia episodes was associated with increasing NPi, based on observed diary episodes (OR 1.7; 95 % CI 1.5, 2.0; $P < 0.001$) and self-reported nocturia rating from questionnaires (OR 1.6; 95 % CI 1.4, 1.9; $P < 0.001$).

36 individuals did not experience regular nocturia (mean number of nocturia episodes < 1). Of these, only six were found to have an NPi of 33 % or higher

A degree of variability was seen between subjects with regards to the extent of NP recorded on each day (intrasubject NPi variability, Table 1).

3.3. Associations between baseline characteristics, fluid intake and nocturnal polyuria

The association between baseline participant characteristics and NPi is summarised in Table 2. A small association was seen between increasing age and NPi. A significant association was also seen between the number of hours asleep and NPi. A link between daily mean fluid intake and NPi was not seen. No significant association was seen between NPi and sex, duration of PD, the number of concurrent urinary symptoms experienced, or the presence of either OSA or antihypertensive/diuretic medications.

Associations were seen for bother related to nocturia (ICIQ mLUTS/fLUTS questionnaire responses) to increase with NPi (OR 1.4; 95 % CI 1.2, 1.6; $P < 0.001$). No significant increase was seen for the overall OABqol score (which includes only a small selection of questions relating to the impact of nocturia) relative to NPi (regression coefficient 0.81; 95 % CI −1.3, 2.9; $P = 0.45$).

3.4. Associations between autonomic symptom profile and nocturnal polyuria

The correlation between NP metrics and $\log_e$ SCOPA-AUT questionnaire responses is shown in Supplementary Table 1. No overall association was seen between total SCOPA-AUT score or urinary subdomain and mean NPi. A significant association was seen between NPi and cardiovascular domain score (log coefficient 0.07; 95 % CI 0.03, 0.11; $P = 0.002$) and a weaker but still significant association was seen for the gastrointestinal domain score (log coefficient 0.05; 95 % CI 0.01, 0.09; $P = 0.03$).

Postural blood pressure measurements were available for 136 participants. A significant trend was seen between overall mean NPi and the presence of orthostatic hypotension (OR 1.2; 95 % CI 1.0, 1.4; $P = 0.03$). Associations with differing NPi levels of nocturnal polyuria and the occurrence of orthostatic hypotension (OH) are displayed in Table 3, with the odds of OH markedly higher with an NPi ≥ 50 %. The association between overall NPi and OH was attenuated in the multi-variable model incorporating age and duration of PD, but the association for high severity NP (NPi > 50 %) remained significant.

A trend for higher NPi was seen with increasing lying systolic blood

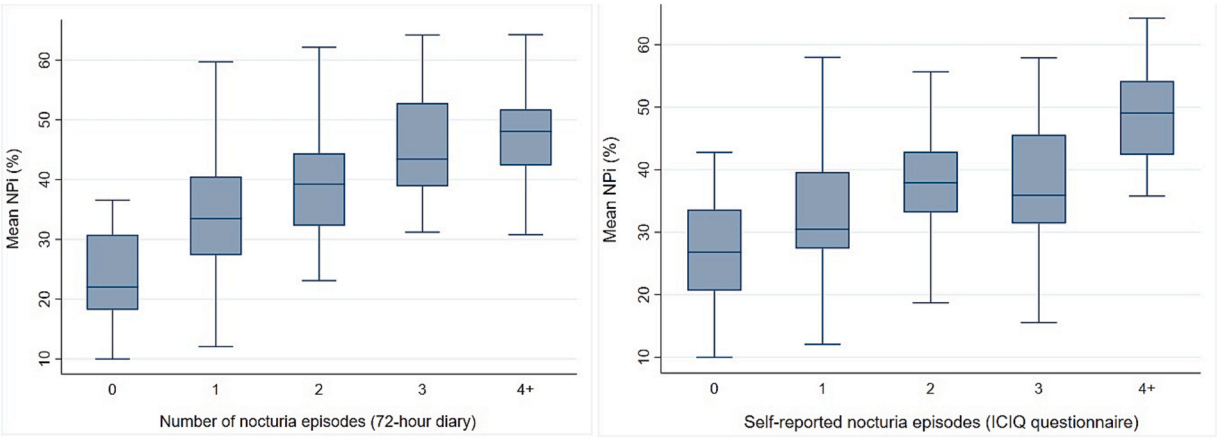

Fig. 1. Box plots demonstrating relationship between mean NPi to nocturia rate from 72-hour diaries (n = 174) and self report from ICIQ mLUTS/fLUTS questionnaire (n = 145).

Table 2
Association between participant characteristics and NPi. NPi = nocturnal polyuria index, OSA = Obstructive sleep apnoea.

Characteristic	Affect on NPi (per 5 % unit)		
	Coefficient	95 % CI	p-value
Female sex	−0.29	−1.0, 0.4	*0.43*
Duration of PD (per year)	0.06	0.0, 0.1	*0.13*
Age (per 5 years)	***0.11***	***0.1, 0.2***	***<0.001***
Hours asleep (per hour)	***0.71***	***0.4, 0.1***	***<0.001***
Total levodopa dose equivalent (per 100 mg)	*−0.01*	*−0.2, 0.1*	*0.90*
Mean fluid intake	−0.03	−0.1, 0.0	*0.26*
OSA	−0.65	−2.3, 1.0	*0.44*
Antihypertensives	0.01	−0.8, 0.8	*0.97*
Diuretics	−2.34	−7.0, 2.3	*0.32*
ICIQ mLUTS symptomatic items	0.06	−0.02, 0.1	*0.16*
ICIQ fLUTS symptomatic items	0.28	−0.1, 0.2	*0.68*

Table 3
Comparison of NPi cut off thresholds and occurrence of orthostatic hypotension, using logistic regression for overall NPi, and ordinal logistic regression model based on NPi severity categories, for both single variable model and multivariable model including age and duration of PD. n = 136 based participants in STRIPE completing postural blood pressure assessment. CI = 95 % confidence interval.

	Occurence of orthostatic hypotension		
	Odds ratio	95 % CI	p-value
Single variable model			
Overall NPi	**1.2**	**1.0, 1.4**	***0.03***
NPi > 33 %	1.0	0.4, 2.9	*0.94*
NPi > 40 %	1.9	0.8, 4.6	*0.15*
NPi > 50 %	**4.9**	**1.6, 15.6**	***0.006***
Multi-variable model			
Overall NPi	1.1	1.0, 1.3	*0.12*
NPi > 33 %	1.0	0.4,2.8	*0.98*
NPi > 40 %	1.6	0.7, 4.1	*0.29*
NPi > 50 %	**4.0**	**1.0, 1.1**	***0.02***

pressure (regression coefficient 1.60; 95 % CI −0.05, 3.2; $P = 0.057$) and diastolic blood pressure (regression coefficient 0.71; 95 % CI −0.06, 1.5; $P = 0.07$), but did not reach statistical significance. No association was seen between categorical presence of supine hypertension and NPi (regression coefficient 0.07; 95 % CI −0.8 0.2; $P = 0.96$).

4. Discussion

Nocturnal polyuria was found to be highly prevalent in this large group of patients with PD experiencing OAB type symptoms. To date, the link between PD and NP has only been assessed in three smaller-scale prevalence studies [5–7]. The NPi definition was assessed in one study of 23 individuals with PD and severe LUTS referred to a specialist service (Smith *et al.* 2015) [5], and another comprising 63 individuals in a general PD clinic with or without LUTS (Romain *et al.*) [6]. Graphic data was also presented on day/night ratio of urine production in a small study of 16 individuals with PD (Hineno *et al.* 1994) [7]. Using the most widely accepted cutoff of NPi33, we demonstrated that 63 % of participants in our study had NP. This compares to reported 78.3 % in the cohort with refractory LUTS (Smith *et al.*) [5], and 64.5 % in the general PD clinic study (Romain *et al.*) [6]. An important limitation of this study is that it is unable to compare to an age-matched non-PD group, which was not included as part of the design of the parent interventional trial. Although the prevalence of NP has been shown to increase with increasing age [20], the Hineno study demonstrated a significant difference between PD patients and 15 control subjects with the former producing larger amounts of night-time urine. Further work to examine this comparison is a key future direction, determining if this is indeed a specific PD-related phenomenon, with well-designed studies using age, sex and ideally co-morbidity matched controls. It is likely that the extent of overall NP is under-estimated using mean values across 72-hour diaries, as differences were seen between mean and maximum observed NPi values, perhaps suggesting that NP can be fluctuant. The variation in impact between differing days was not explored.

A key finding of this study is the association between autonomic cardiovascular instability (presumed in these patients to be a consequence of their PD) and increasing extents of NP. A significant association was seen between the overall mean NPi and the categorical presence of OH based on established definition, with each 5 % NPi increase raising the odds of having defined postural hypotension by 20 %. Further breaking this down into specific NPi severity categories, a non-significant trend for increasing odds of OH was seen at the 40 % threshold, but at the 50 % threshold the odds ratio increased to 4.9 and became highly significant. Interestingly the cardiovascular domain of SCOPA-AUT, which reports subjectively experienced symptoms, was also associated with mean NPi, further reinforcing a link between NP and cardiovascular function [2]. This is particularly important given that OH may be asymptomatic in some patients. One key issue that stands out is that the presence of OH was determined categorically with regards to the fall on standing being in excess of consensus criteria [16], however great variability can be seen between both extent of quantitative fluctuations and degree of symptom burden experienced.

No association was found between longer durations of PD and NP, fitting with the increasing recognition of multiple phenotypes seen in PD, rather than symptom burden simply being a function of disease duration. A small but highly significant association was seen between age and NPi which matches other studies of general populations. When using a multi-variable model incorporating age and duration of PD, the link between overall NPi and OH became non-significant, but the association with between severe NPi (>50 %) and OH remained significant, suggesting an association beyond just that with age. It is likely that powering affected the strength of these associations, as well as the use of a homogenizing dichotomous OH variable.

The link between blood pressure lability and nocturia has not been assessed previously in PD, and is a strong area of potential interest for exploring the mechanisms behind nocturnal polyuria in PD. In general populations, a link between cardiovascular disease and nocturia is well established [21], with features such as leg oedema and impaired venous return contributing to nocturia by increasing renal perfusion on eliminating gravity on lying flat at night. In non-PD idiopathic NP populations, both hypertension and the loss of physiological night-time blood-pressure dip are disproportionately seen [22]. Frank supine hypertension is well recognised in PD, affecting around 27.8 % in a *meta*-analysis of blood pressure studies [23]. Our study also showed a trend towards increasing NPi with rising lying blood pressure, although was likely under-powered to demonstrate this effect. The sustained impact of blood pressure over the course of a long-period recumbent (as with a period asleep) was not assessed, as the readings were taken only from a day-time single clinic visit.

Several possible mechanisms involving autonomic control could the explain the association seen in our study. Impaired control of systemic vascular tone could lead to venous pooling, with fluid collecting in the daytime returning to the central circulation at night when recumbent, leading to excessive renal perfusion. An alternative is that the link seen is simply an association with having more severe autonomic disease in general and systemic cardiovascular dysfunction does not play a direct role in driving nocturnal polyuria or is only a single contributory component. It is possible that a more specific loss of nuanced control of renal glomeruli may occur, with loss of sensitivity to the signals that control well described physiological circadian fluctuations of renal function seen at night [24]. This could relate to dysfunction of direct renal sympathetic innervation, or through abnormalities of circadian mechanisms such as melatonin regulation which are described in PD [25]. There may also be a circular association between renal perfusion/filtration abnormalities in PD and cardiovascular lability, with each worsening the other.

Another possible cause of NP in PD may be related to OSA, which has been demonstrated to cause nocturnal ANP release that promotes naturesis in non-PD populations [26]. No association was found between NP and OSA in this study, however the number reporting OSA was very low (4.5 %) which would affect power to measure this association. Attribution of OSA status was based solely on self-reported diagnosis or clinical records, rather than prospective overnight oximetry and did not include features such as severity or treatment details, which would be important to assess in a future study. The link between PD and OSA is enigmatic, with a recent *meta*-analysis suggesting OSA is an independent risk factor for developing PD [27]. However, OSA rates are not higher in those with established PD. These data are limited (from 12 studies) and the diagnosis of OSA was often based on retrospective referrals for OSA assessment. Given the strong link between OSA and NP outside of PD, prospective exploration of this link would be pertinent. We did not find an association between nocturia and the use of anti-hypertensives or diuretics, recognising again that this represented a relatively low number of participants affecting power. The effect of night-time dopaminergic medication sustained release preparations was not assessed and data on peripheral oedema or body-mass index was not systematically collected due to the nature of this being a sub-study of the main interventional trial, but would be important for future studies. The overall differential impact of varying types of PD medications (eg. Levodopa vs dopamine agonist), the use of sleep inducing medication such as melatonin and the association with other non-motor symptoms such as cognition was not assessed in this study due to a lack of power, however would be important considerations for future specifically designed trials on nocturia in PD. Furthermore, objective assessment of sleep architecture and NP's effect on this would be of great interest, although outside the scope of this sub-study.

Further limitations of this sub-study were that formal urodynamic assessment was not performed, which was not included as part of the protocol given its semi-invasive nature, and the fact that NP is unlikely to be reflected during urodynamics, although could be helpful to correlate phenotype. Specific assessment of sexual function was only undertaken using the SCOPA-AUT sub-score, with no association found, however the use of a specific scoring system could be more sensitive. Finally, the collection of urine volumes as part of a 72-hour bladder diary, whilst objective, is highly dependent on the patient to ensure accuracy, and can be affected by issues such as cognition or dexterity.

Another important finding of this study was that the number of observed nocturia episodes increased with higher NPi values. The finding of NP being causative in nocturia has been well established in non-PD populations [28], however in PD the influence of OAB is present, which can also lead to nocturia by causing lower storage capacity with a lower threshold of sensation to void. The component of NP is likely sizeable, with the level of NP rising in a consistent trajectory with an increasing number of nocturia episodes. It is important to appreciate that this association remained strong despite being undertaken within a cohort by definition entirely selected to be symptomatic of daytime OAB for the main trial. NP was also clearly linked to impact on quality of life, with each 5 % rise in NPi increasing the odds of a point increase in bother (on a 0–10 score) by 40 %. These points emphasise that NP is therefore important to diagnose, and treatment will be different between diminishing excessive urine production and stabilising OAB. The use of a 72-hour bladder diary required to diagnose NP is cheap and generally acceptable to patients and should therefore be a first line tool for clinicians caring for people with PD and nocturia. With multiple metrics used to define NP, the diagnosis of clinically significant NP perhaps should comprise a composite of clinical impact (with > 2 episodes per night routinely considered significant), coupled with a quantitative threshold such as NPi > 33 %.

The vast majority of existing interventional trials for LUTS in PD have sought to address OAB, and therefore further work is needed to develop strategies to improve NP in this group [29]. A number of early-stage trials have explored the potential role of agents that may have a role on nocturnal urine production including the use of desmopressin and melatonin [30,31]. Desmopressin has a long-standing history as a treatment for nocturia, and works by increasing absorption in the renal collecting duct, therefore reducing the volume of urine reaching the bladder. One major question regarding desmopressin is concern over hyponatraemia leading to adverse symptoms [32], common particularly in older individuals representing many of those with PD. Low dose desmopressin treatment may partially mitigate this risk and be better tolerated in older individuals [33]. The mechanisms that mediate a reduction in NP with melatonin are as yet enigmatic, but an abnormal pattern of melatonin secretion has been demonstrated in PD [25], which might influence pathways controlling the physiological "renal clock".

5. Conclusion

We demonstrated that nocturnal polyuria was highly prevalent in a cohort of PD patients, the majority of whom had OAB symptoms, whilst acknowledging the limitations of missing a healthy comparator cohort. Greater severity of NP is associated with an increasing rate of nocturia, suggesting that NP is an important component driving this symptom. Association with both objective markers and subjective symptoms of orthostatic hypotension were seen with increasing NP. This suggests that

the origin of NP is likely autonomic and may even be directly related to effect of BP lability on renal perfusion. Future studies should address potential interventions to help with this burdensome symptom and further describe the relationship between BP variation and nocturia.

Ethical approval

Full ethics board permission was acquired for this study as part of the STRIPE parent trial from the Camden and Kings Cross Research Ethics Committee (Reference number 21/LO/0418).

CRediT authorship contribution statement

Matthew D Smith: Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Anisha Cullen:** Writing – review & editing, Investigation. **Gabriella E Portlock:** Writing – review & editing, Investigation. **Marcus J Drake:** Writing – review & editing, Methodology. **Yoav Ben-Shlomo:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Emily J Henderson:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Formal analysis, Conceptualization.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Emily J. Henderson reports financial support was provided by Gatsby Charitable Foundation. Matthew Smith reports a relationship with AbbVie Inc that includes: speaking and lecture fees. Emily J. Henderson reports a relationship with Simbec-Orion Group Limited that includes: consulting or advisory. Emily J. Henderson reports a relationship with Curatio CME Institute that includes: consulting or advisory. Emily J. Henderson reports a relationship with Kyowa Kirin Inc that includes: speaking and lecture fees. Emily J. Henderson reports a relationship with Bial that includes: speaking and lecture fees and travel reimbursement. Emily J. Henderson reports a relationship with Elsevier Inc that includes: speaking and lecture fees. Emily J. Henderson reports a relationship with Parkinson's Academy that includes: speaking and lecture fees. Emily J. Henderson reports a relationship with AbbVie Inc that includes: speaking and lecture fees and travel reimbursement. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author roles

MS designed and executed the study, undertook analysis and wrote the final manuscript. AC and GP executed the study and edited the manuscript. MD designed the study and edited the manuscript, YBS and EH designed the study, assisted in analysis and edited the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.prdoa.2025.100334.

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