

ORIGINAL ARTICLE

Exploratory pilot study of exogenous sustained-release melatonin on nocturia in Parkinson's disease

Amit Batla¹  | Sara Simeoni^{2,3} | Tomoyuki Uchiyama² | Lorenzo deMin² | Joanne Baldwin² | Charles Melbourne² | Saiful Islam | Kailash P. Bhatia¹ | Mahreen Pakzad² | Sofia Eriksson | Jalesh N. Panicker^{2,3}

¹Department of Clinical and Movement Neuroscience, UCL Queen Square Institute of Neurology, London, UK

²Department of Uro-Neurology, The National Hospital for Neurology and Neurosurgery, London, UK

³Department of Brain Repair and Rehabilitation, Faculty of Brain Sciences, University College London Queen Square Institute of Neurology, University College London, London, UK

Correspondence

Amit Batla, Department of Clinical and Movement Neuroscience, UCL Queen Square Institute of Neurology, London, UK.

Email: a.batla@ucl.ac.uk

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Abstract

Introduction: Nocturia is one of the commonest non-motor symptoms in Parkinson's disease (PD). Nocturia has evolved from being understood as a symptom of urological disorders or neurogenic bladder dysfunction to being considered as a form of circadian dysregulation. Exogenous melatonin is known to help circadian function and can be an effective strategy for nocturia in PD.

Methods: In this open-label, single-site, exploratory, phase 2 pilot study, adults with PD and nocturia underwent assessments using standardized questionnaires, urodynamics studies and a bladder scan. This was followed by completion of a frequency volume chart (FVC) and 2-week sleep diary. Sustained-release melatonin 2 mg was then administered once-nightly for 6 weeks. A repeat assessment using questionnaires, the FVC and sleep diary was performed whilst on treatment with melatonin. Companion or bed partners filled in sleep questionnaires to assess their sleep during the intervention.

Results: Twenty patients (12 males; mean age 68.2 [SD = 7.8] years; mean PD duration 8.0 [\pm 5.5] years) with PD reporting nocturia were included. Administration of melatonin was associated with a significant reduction in the primary outcome bother related to nocturia measured using the International Consultation on Incontinence Questionnaire Nocturia (ICIQ-N) ($p = 0.01$), number of episodes of nocturia per night ($p = 0.013$) and average urine volume voided at night ($p = 0.013$). No serious adverse events were reported. No significant improvement was noted in bed partner sleep scores.

Conclusions: In this preliminary open-label study, administration of sustained-release melatonin 2 mg was found to be safe for clinical use and was associated with significant improvements in night-time frequency and nocturnal voided volumes in PD patients.

KEYWORDS

circadian, melatonin, nocturia, Parkinson's disease, sleep

Amit Batla and Sara Simeoni contributed equally to this work.

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INTRODUCTION

Nocturia is the most commonly reported non-motor symptom in Parkinson's disease (PD) [1-3] and negatively impacts quality of life, affecting both patients and their carers.[4,5] Nocturia has been shown to be an important risk factor for falls and for sustaining fractures,[6] and is associated with greater cardiovascular morbidity [7] and mortality.[8] The mechanisms responsible for nocturia are uncertain; however, pathophysiological underpinnings include reduced bladder capacity, most commonly from detrusor overactivity, and increased night-time urine production, known as nocturnal polyuria (NP).[9] Specifically in PD, impairment of circadian regulation or autonomic dysfunction with nocturnal redistribution across the extracellular fluid compartments are likely contributors to nocturia.[10] The treatment options for managing nocturia are limited and include use of a daytime diuretic or desmopressin.[11,12]

Circadian rhythm disturbances are common in PD and lead to sleep disturbance, insomnia and excessive daytime sleepiness.[13] The suprachiasmatic nucleus (SCN) is the seat of neurological regulation of the circadian rhythm. Melatonin is a hormone secreted from the pineal gland in response to dark that provides feedback to the SCN and helps to synchronize the circadian rhythm by affecting both the phase and amplitude of rhythmic neuronal firing.[14,15] The concept of nocturia has evolved from being a symptomatic aspect of urological disease to a form of circadian dysfunction [16] Moreover, studies have demonstrated an inverse relationship between melatonin levels and degree of nocturia.[17] Exogenous administration of melatonin has been shown to be effective in reducing night-time frequency and improve quality of life in the elderly.[18] A significant improvement in night-time frequency and nocturia-related bother was demonstrated in a cohort of men with lower urinary tract (LUT) symptoms with benign prostate enlargement.[19] Exogenous melatonin has not been evaluated in neurodegenerative disorders and the aim of this study was to explore the feasibility and efficacy of exogenous melatonin administration for the management of nocturia in PD, and the impact this has on carers.

METHODS

In this open-label, single-site, exploratory, phase 2b pilot study, patients with a clinical diagnosis of PD (Queen Square Brain Bank criteria [20]) age >18 years and reporting more than two episodes of nocturia as per the Non-Motor Symptoms Questionnaire (NMSQuest) item 9, "Getting up regularly at night to pass urine", [21] were included. The study was approved by the National Research Ethics Service Committee London - Hampstead (REC Reference No. 15/LO/0441). All patients and carers participating in the study were provided with written information and informed consent was obtained, and the trial adhered to the CONSORT statement. Patients with cognitive impairment, a history suggestive of rapid eye movement (REM) sleep behaviour disorder, congestive heart failure, liver failure or kidney failure, uncontrolled diabetes, presence of urinary

tract infection, incomplete bladder emptying or presence of significantly enlarged prostate were excluded. The detailed selection criteria (inclusion and exclusion) and plan of study visits and investigations are provided in Appendix 1.

Patients completed the following questionnaires and diaries:

- ICIQ-N (International Consultation on Incontinence Questionnaire- Nocturia) is a validated tool for evaluating nocturia frequency as well as nocturia-related bother.[22]
- Urinary Symptom Profile (USP) is a standardized questionnaire assessing LUT symptoms in terms of Overactive Bladder (OAB), Low Stream (LS) and Stress Incontinence (SI) symptoms.[23]
- SF Qualiveen is an eight-item validated questionnaire that evaluates LUT symptoms-related quality of life.[24]
- EQ-5D is a standardized questionnaire evaluating generic health status and quality of life.[25]
- PD Sleep Scale (PDSS) [26] and Pittsburgh Sleep Quality Index [27] are standardized sleep questionnaires that have been validated to capture sleep-related parameters and quality of sleep.
- Three-day frequency volume chart (FVC) that recorded voiding times, fluid intake and respective volumes. The nocturnal polyuria index (NPI) was calculated as nocturnal urine volume (NUV) divided by 24-hour urine volume and is normally <33%.
- A 14-day sleep diary was used to record the number of awakenings at night.

Participants underwent urodynamics studies performed according to International Continence Society (ICS) Good Urodynamic Practice [28] including uroflowmetry, filling cystometry and pressure flow study. After completing the questionnaires and diaries, patients were administered sustained-release melatonin 2 mg (Circadin™; Flynn Pharma Ltd, Stevenage, UK) that was taken once-nightly for 6 weeks. Compliance was assessed by weekly telephone calls by the research nurse and adverse events were recorded.

Patient carers or bed partners recruited to the study completed the Pittsburgh Sleep Quality Index and a 14-day sleep diary.

The primary outcome evaluated was nocturia-related bother and the secondary outcomes were safety, number of nocturia episodes per night, voided volumes at night, other lower urinary tract symptoms, sleep disturbances and quality of sleep, quality of life and sleep disturbance in partners.

Statistical plan

This was a pilot study, and in the absence of clinical studies evaluating the effects of treatment on nocturia in PD, no sample size could be calculated.

Statistical analysis was performed using SPSS 22 software (SPSS Inc., Chicago, IL, USA).

Normality of data was checked at baseline and after intervention. If data were normally distributed, differences between the outcome measures at baseline and post-intervention were compared using

the two independent sample t-test. If at least one variable (baseline or post-intervention) was not normally distributed, differences between the outcome measures at baseline and post-intervention were compared using the non-parametric Wilcoxon signed-ranked test. Differences were considered statistically significant for p values <0.05 .

RESULTS

Twenty patients (12 males; aged 68.2 [± 7.8] years) with PD disease and nocturia completed the study and were included in the analysis (Figure 1). Duration of PD was 8.0 (SD = 5.5) years. The Hoehn and Yahr (H&Y) score was 2 (SD = 0.6). The mean PDSS score at baseline was 92.16 (SD = 25.88). Looking at questions 2 and 3 of the PDSS that are used for insomnia, the percentage of patients who scored <5 on question 2 was 30% (6/20) and on question 3 was 55% (11/20).

Primary outcomes

Administration of melatonin was associated with a significant reduction in bother related to nocturia measured using the ICIQ-N with a decrease in the score from 7 ± 2.08 at week 0 to 4 ± 2.6 at week 6 ($p = 0.01$) (Table 1).

Secondary outcomes

After treatment with melatonin, a significant improvement in sleep quality, reduction of sleep onset latency ($p = 0.024$), number of awakenings ($p = 0.001$) and sleep quality ($p = 0.033$) were observed in the sleep diaries ($n = 20$). The first uninterrupted sleep period between

bedtime and first awakening based on the sleep diary mildly improved (median 8 min), which did not reach statistical significance.

PDSS questionnaires after treatment showed that patients experienced a significant improvement in overall quality of sleep (score for question 1 of PDSS, $p = 0.015$), reduced difficulty in falling asleep each night (score for question 2, $p = 0.027$), reduced restlessness of legs or arms causing disruption of sleep (score for question 4, $p = 0.009$), a significant reduction in the number of episodes of nocturia (score for question 8, $p = 0.006$) and a significant improvement in the tiredness/sleepiness after waking in the morning (score for question 14, $p = 0.022$) (Table 2).

Use of melatonin was associated with a significant reduction in the number of episodes of nocturia per night measured with ICIQ-N score ($p = 0.013$) and a significant reduction in the average urine volume voided at night ($p = 0.013$), measured using FVCs ($n = 16$). There was no significant change in the NPi (Table 1).

A multivariate logistic regression analysis was performed to identify if there were any factors that could predict the response to melatonin, defined as improvement in bother related to nocturia measured using the ICIQ-N. The following variables were included in the model: age, gender, duration of PD, severity of PD measured using H&Y, severity of sleep disorder measured using the PDSS, NPi, severity of urinary dysfunction measured using the USP, quality of life measured using the SF Qualiveen, presence or absence of detrusor overactivity on urodynamics, and severity of nocturia at baseline. The model was not statistically significant ($p > 0.05$).

No serious adverse events were reported. Reported side effects included paraesthesia ($n = 1$; 5%), nightmares ($n = 1$; 5%), nausea ($n = 1$; 5%), tiredness ($n = 1$; 5%) and stiffness of the back ($n = 1$; 5%). One patient discontinued melatonin because of insomnia.

Ten carers completed sleep diaries. Sleep diaries revealed no significant changes in sleep onset, number and duration of awakenings, and sleep quality (all $p > 0.05$) between week 0 and week 6 of the intervention.

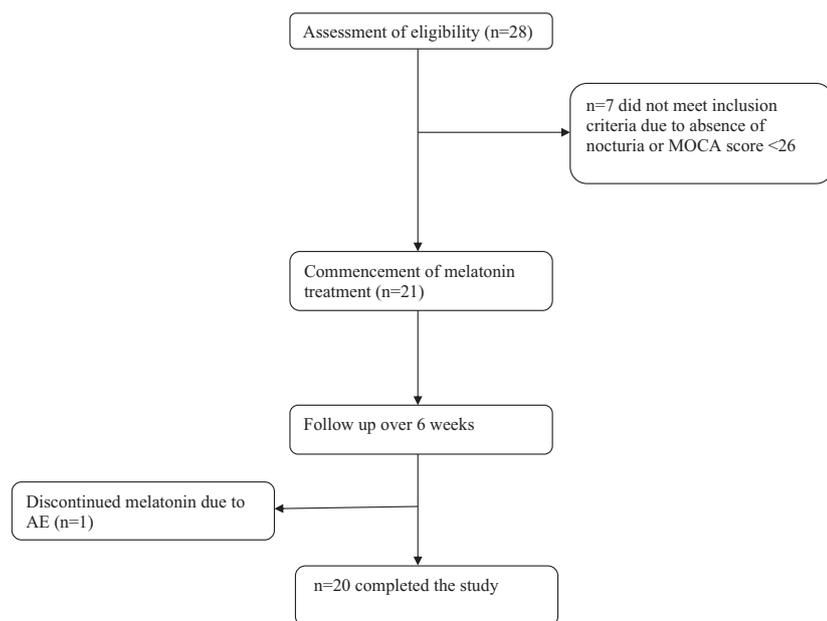


FIGURE 1 CONSORT flow diagram depicting enrolment of participants and the intervention. AE, adverse event; MOCA, Montreal Cognitive Assessment.

TABLE 1 Changes in lower urinary tract parameters following administration of melatonin 2 mg for 6 weeks

Outcome measure	Baseline	6 weeks	p value
Nocturia-related bother (ICIQ-N)	7 (2.08)	4 (2.6)	0.01
ICIQ-N night-time frequency (ICIQ-N)	3.0 (0.87)	2.0 (0.95)	0.013
USP (total score)	11.0 (4.64)	8.0 (4.09)	0.374
SFQ	1.25 (0.79)	1.13 (0.55)	0.276
Nocturnal polyuria index (NPI) ^a	0.47 (0.14)	0.425 (0.13)	0.214
Mean frequency of night-time voids ^b	3.00 (1.76)	1.67 (1.25)	0.09
Bladder sensation ^b	2.56 (0.7)	2.39 (0.8)	0.27
Average urine volume produced during night (ml) ^b	926.67 (362.28)	625.86 (272.63)	0.013

Note: Figures in bold type denote statistical significance.

Abbreviations: FVC, frequency volume chart; ICIQ-N, International Consultation on Incontinence Questionnaire-Nocturia; NPI, nocturnal polyuria index; SFQ, SF Qualiveen; USP, Urinary Symptom Profile.

^aNPI is calculated from the 3-day frequency volume chart (FVC) as the total urine volume voided during the night (including the first void in the morning) divided by the urine volume voided over 24 hours. Data were available for $n = 16$; four patients did not complete the FVC correctly.

^bNight-time voids and urinary volume was derived from 3-day FVC. Data were available for $n = 16$; four patients did not complete the FVC correctly.

DISCUSSION

The results of this open-label pilot study suggest that the use of low-dose sustained-release melatonin was associated with improvement of the primary outcome, namely nocturia-related bother. Melatonin reduced night-time urinary frequency as per the questionnaire. These improvements were associated with improvements in different sleep parameters. There was no impact on daytime symptoms.

In health, a reduction of urine production nocturnally is mediated by alterations in sodium handling. Moreover, a greater bladder storage capacity at night accommodates urine that is produced.[17] This ensures that sleep is not disturbed by the need to void. Nocturia can result from reduced bladder capacity due to poor compliance or detrusor overactivity. In PD, nocturia can also result from NP and in an earlier study we reported an NPI as high as 0.81 (normal <0.33).[29] NP can be associated with increased solute excretion (osmotic diuresis) or excessive free water clearance [30] NP is uncertain and increased nocturnal urine production has been found to be associated with raised daytime arterial blood pressures and reduced plasma levels of angiotensin II and arginine vasopressin.[31] Natriuresis at night was attributed to suppressed levels of plasma angiotensin II.[31]

Though this open-label study was not designed to determine the mechanisms underpinning this improvement, the reduction of nocturnal voided urine volumes suggests the benefit could be due to reduced urinary volume at night possibly through the effects of melatonin on circadian control. The SCN regulates the central circadian clock,[15] and also entrains peripheral clocks in different visceral organs including the kidneys.[30] Renal sodium and water excretion is regulated by circadian biological rhythms and the 20-HETE

synthesis pathway is one of the principal renal targets.[32,33] Proteins associated with the 20-HETE synthesis pathway are involved in the regulation of the renal transport genes and thereby can modulate the circadian fluctuations in renal excretion.[33] Feedback from the renal clock influences activity of the SCN, and thereby the central circadian rhythm.[11] The neuroendocrine feedback loop that regulates the circadian rhythm is altered in neurodegenerative disorders. Sleep disturbances in PD are well described to be related to circadian dysregulation [34] and synuclein-containing inclusions have been shown in the SCN.[13] Melatonin has been used in patients with PD to manage insomnia, and a significant improvement in subjective sleep disturbances and total sleep time measured using actigraphy has been demonstrated with favourable tolerance profiles.[35]

Systematic studies evaluating night-time urine production in PD are lacking; however, increased melatonin levels have been shown to be negatively correlated with autonomic non-motor symptoms in PD including sleep disorders, gastrointestinal and cardiovascular autonomic symptoms.[36] Furthermore, it has been suggested that melatonin may have neuroprotective effects, altering the course of disease progression in animal models.[37,38]

The effects of melatonin on LUT functions are, however, less clear. Exogenous administration of melatonin has been shown to ameliorate bladder dysfunction in guinea pigs [39] and improvement of detrusor overactivity in rats.[40] Melatonin has been shown to inhibit acetylcholine- and potassium chloride-induced contractions in isolated bladder strips from guinea pigs [39] In a cystometry study of female Sprague Dawley rats, melatonin significantly increased bladder capacity in a dose-dependent manner.[40] A randomized, double-blind, placebo-controlled crossover study of

TABLE 2 Changes in sleep parameters following administration of melatonin 2 mg per patient (n=20) for 6 weeks based on sleep diary and Parkinson's Disease Sleep Scale

Outcome measure	Baseline	6 weeks	p value
Sleep onset (min)	23.63 (31.53)	17.68 (18.35)	0.024
Number of awakenings	2.42 (0.79)	1.97 (0.89)	0.001
Duration of awakenings (min)	15.91 (10.14)	14.54 (7.3)	0.053
Sleep duration (h)	6.85 (1.5)	7.2 (1.13)	0.277
First uninterrupted sleep period (FUSP) (min)	177 (65)	185 (41.25)	0.851
Quality of sleep	2.14 (0.41)	2.33 (0.45)	0.033
Total PSQI score	8.5 (5.81)	10.5 (4.0)	0.158
PDSS questions			
Q1. The overall quality of night's sleep is (0 for awful/to 10 for excellent)	5.25 (1.9)	7.0 (2.10)	0.015
Q2. Do you have difficulty falling asleep each night? (scored from 0 for always/frequent to 10 for never)	7.75 (2.78)	8.0 (2.53)	0.027
Q3. Do you have difficulty staying asleep? (scored from 0 for always/frequent to 10 for never)	3.0 (2.7)	5.75 (3.02)	0.069
Q4. Do you have restlessness of legs or arms at night or in the evening causing disruption of sleep? (scored from 0 for always/frequent to 10 for never)	7.0 (3.24)	8.75 (1.83)	0.009
Q8. Do you get up at night to pass urine? (scored from 0 for always/frequent to 10 for never)	0.5 (0.8)	1.0 (2.6)	0.006
Q14. Do you feel tired and sleepy after waking in the morning? (scored from 0 for always/frequent to 10 for never)	3.5 (2.27)	6.0 (3.02)	0.022
PDSS total score	92.16 (25.88)	100.48 (40.25)	0.10

Figures in bold type denote statistical significance

Abbreviations: PDSS, Parkinson's Disease Sleep Scale; PSQI, Pittsburgh Sleep Quality Index).

controlled release melatonin 2 mg performed in 20 men with urodynamically confirmed bladder outflow obstruction due to benign prostate enlargement demonstrated a significant improvement in nocturia frequency and nocturia-related bother, without any significant side effects reported.[19] Administration of 2 mg melatonin

in a randomized controlled trial or of individuals reporting nocturia demonstrated reduced night-time urinary frequency and improved quality of life scores.[18]

The results of this open-label study are preliminary but suggest that repurposing melatonin for treating nocturia is a safe and feasible option, particularly in neurodegenerative disorders associated with circadian rhythm disturbances.[41] There was a very low drop rate and patient compliance was high and side effects were uncommon and mild. Furthermore, no significant changes were reported to the patient's response to dopaminergic medication. Higher dosages have been tried for other indications such as REM sleep behaviour disorders (ranging between 3 and 12 mg) [42] and sleep disorders (up to 50 mg) [35] in PD without significant adverse effects and therefore future studies should explore a dose-response relationship between melatonin and changes in nocturnal voiding parameters. An open-label design and small number of patients are limitations; however, the study affirms the need for a properly powered placebo-controlled randomized study to confirm these findings, and to explore whether the effects of melatonin were through changes in the circadian regulation or improvements in functional bladder capacity. The logistic regression model we applied did not show any significant predictors that could help distinguish the responders from non-responders. Though this could be true, it appears that the sample size was too small for such an association to be established. Future studies could explore the pathophysiology underpinning the relationship between circadian dysregulation and nocturia in PD and aim to establish predictors of response to melatonin. This can be achieved by using specific biomarkers for circadian rhythm that might correlate with nocturia. Lastly, the correlation between improvements in nocturia with other non-motor symptoms should also be evaluated.

The results from this preliminary open-label study provide pilot data that lend credence to the hypothesis that nocturia in PD could be contributed by circadian disturbance. Larger double-blind placebo studies are needed before proposing use of melatonin as the treatment for nocturia in PD.

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CONFLICT OF INTEREST

A.B. has received speaker honoraria from Ipsen Pharma and receives royalties from the book *Understanding Parkinsonism*

(Jaypee Brothers, 2017). He reports no disclosures related to this work. K.P.B. has received honoraria from Ipsen, Allergan, GE and Neuroderm. He has received personal compensation in an editorial capacity for MDS and royalties for book editing from OUP. He has no disclosures related to this work. J.N.P. has received honoraria from Novartis and Wellspect. He has received royalties for book editing from Cambridge University Press. He has no disclosures related to this work. S.S. has no disclosures related to this work.

AUTHOR CONTRIBUTIONS

Amit Batla: Conceptualization (equal); Data curation (supporting); Formal analysis (equal); Funding acquisition (equal); Investigation (equal); Methodology (equal); Project administration (equal); Resources (supporting); Software (supporting); Supervision (equal); Validation (equal); Visualization (supporting); Writing-original draft (lead); Writing-review & editing (equal). **Sara Simeoni:** Data curation (equal); Formal analysis (lead); Investigation (supporting); Project administration (equal); Resources (equal); Supervision (supporting); Validation (equal); Visualization (supporting); Writing-original draft (equal); Writing-review & editing (supporting). **Tomoyuki Uchiyama:** Formal analysis (equal); Project administration (supporting); Software (equal); Validation (equal); Writing-review & editing (supporting). **Lorenzo De Min:** Investigation (equal); Methodology (equal); Project administration (equal); Software (supporting); Writing-review & editing (equal). **Maria Joanne Baldwin:** Data curation (equal); Project administration (equal); Resources (equal); Software (supporting); Writing-review & editing (supporting). **Charles Melbourne:** Formal analysis (equal); Project administration (supporting); Resources (supporting); Writing-review & editing (supporting). **Saiful Islam:** Formal analysis (supporting); Methodology (supporting); Software (equal); Validation (supporting); Writing-review & editing (equal). **Kailash P. Bhatia:** Conceptualization (supporting); Funding acquisition (supporting); Methodology (supporting); Project administration (supporting); Supervision (supporting); Validation (equal); Writing-review & editing (equal). **Mahreen Pakzad:** Methodology (supporting); Project administration (supporting); Resources (equal); Supervision (supporting); Validation (supporting); Writing-review & editing (supporting). **Sofia Eriksson:** Funding acquisition (supporting); Investigation (supporting); Project administration (supporting); Resources (equal); Supervision (supporting); Validation (equal); Writing-review & editing (equal). **Jalesh N. Panicker:** Conceptualization (lead); Data curation (lead); Formal analysis (equal); Funding acquisition (lead); Investigation (equal); Methodology (equal); Project administration (lead); Resources (lead); Software (equal); Supervision (lead); Validation (equal); Visualization (equal); Writing-original draft (supporting); Writing-review & editing (lead).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in the supplementary material of this article (Appendix 1). Further data that support the findings of this study are available from the corresponding author upon reasonable request. The trial was registered

with EudraCT (Reference: 2014-002697-37) and ClinicalTrials.gov (Identifier: NCT02359448). The study data and results are available in the public domain.[43]

ORCID

Amit Batla  <https://orcid.org/0000-0001-8952-2160>

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APPENDIX 1

SELECTION OF SUBJECTS

1.1 Inclusion criteria

1. Adults (>18 years) with clinically diagnosed Parkinson's disease (PD) according to the Brain Bank Criteria.[44]
2. Reporting nocturia to Non-Motor Symptoms Questionnaire (NMSQuest) item 9 "Getting up regularly at night to pass urine" [21] and getting up to pass urine two or more times at night. Although the International Continence Society (ICS) defines nocturia as waking up at night one or more times to void,[45] a recent population-based study has shown that two voids or more is associated with bother and impaired health-related quality of life. [46,47]
3. Able to provide informed written consent.

1.2 Exclusion criteria

1. Cognitive impairment as assessed by the Montreal Cognitive Assessment (MOCA) (score <26).
2. History suggestive of rapid eye movement (REM) sleep behaviour disorder.
3. Congestive heart failure, liver failure or kidney failure.

4. Uncontrolled diabetes, or significant microalbuminuria in patients with diabetes.
5. Using medications such as benzodiazepines or Z-drugs (e.g., Zaleplon, Zolpidem and Zopiclone).
6. Presence of urinary tract infection as determined by the clinician.
7. Evidence for incomplete bladder emptying (i.e., post-void residual urine of more than 100 ml as determined by ultrasound (bladder scan)).
8. Presence of significantly enlarged prostate as determined by the clinician using the European Association of Urology (EAU) guidelines based on urodynamic findings.[48]
9. Females of childbearing potential must be willing to use an effective method of contraception (hormonal or barrier method of birth control; abstinence) from the time of consent is signed until 6 weeks after treatment is discontinued.
10. Females of childbearing potential must have a negative pregnancy test within 7 days prior to being registered for trial treatment.
11. Females must not be breastfeeding.
12. Allergies to excipients of Investigational Medicinal Product (IMP).
13. Smokers.
14. Patient with autoimmune disease.
15. Patients taking carbamazepine, rifampicin and cimetidine.
16. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or galactose malabsorption.
17. Excessive alcohol consumption as defined by the investigator.

FIGURE A1 Study time line

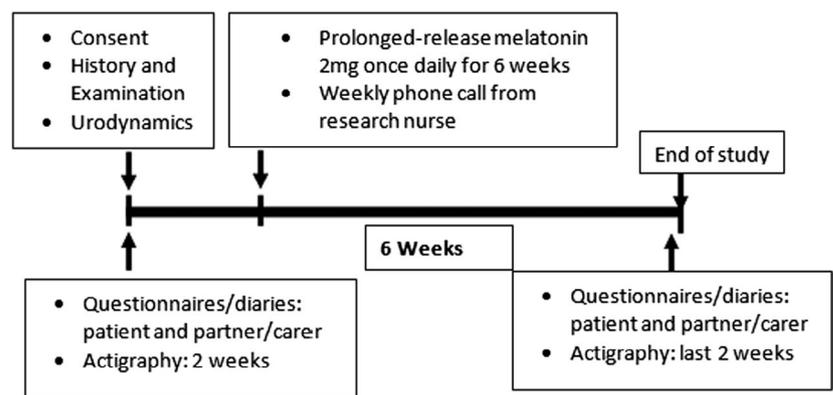


TABLE A1 Details of study visits and phone calls

	Visit 1- (week 0) Screening and informed consent	Visit 2- (week 3) Commencement of melatonin 14 days after visit 1	Weeks 3 to 8 - Weekly phone call monitoring No visit	Visit 3 (week 8) Follow up Week 8/Early discontinuation visit
Informed consent: patient and partner/carer	X			
Medical history/physical exam including neurological examination	X			
Vital signs including weight	X			X
Concomitant medication review	X		X	X
Questionnaires (ICIQ-N, USP, SF Qualiveen, EQ5D, PDSS, Pittsburgh Sleep Quality Index)	X			X
Frequency volume chart for 3 days	X		X	
Sleep diary for 2 weeks	X (weeks 1 and 2)		X (weeks 7 and 8)	
Partner/carer sleep diary (2 weeks) and questionnaire (Pittsburgh Sleep Quality Index)	X (weeks 1 and 2)		X (weeks 7 and 8)	
Pregnancy test (if appropriate)		X		
Urine dipstick (to exclude UTI)		X		X
Urodynamics	X			
Accelerometer (for actigraphy) for 2 weeks	X (weeks 1 and 2)	X (weeks 7 and 8)		
IMP dispensed		X		
IMP count				X
AE review	X	X	X (weekly)	X