Sleep and Overactive Bladder in Parkinson's Disease

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KEYWORDS

• Nocturia • Parkinson's disease • Overactive bladder • LUTS • Sleep disturbances

KEY POINTS

- Nocturia and overactive bladder (OAB) are prevalent in patients with Parkinson's disease (PD) due to the bladder physiology changes and sleep disturbances associated with PD.
- The complex interplay of poor sleep quality, nocturia, and OAB lead to increased fall risk in patients with PD and severely impact not only their quality of life (QoL) but also QoL of their bed partners.
- Nocturia in patients with PD is multifactorial and often related to sleep disturbances from PD.
- Management of these patients requires a careful assessment of their PD status, available support structure, and tailoring of therapy that is feasible and effective.
- A multidisciplinary approach including neurologist, urologist, and sleep specialist should be considered to maximize treatment strategies for nocturia and OAB.

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra leading to classic motor symptoms such as resting tremors, bradykinesia, rigidity, and postural instability. While significant progress has been made in addressing these motor dysfunctions, nonmotor symptoms are increasingly recognized as critical to the quality of life (QoL) in patients with PD[1] (**Fig. 1**). These include olfactory dysfunction, neuropsychiatric symptoms (depression, anxiety, and so forth), autonomic dysfunction (orthostatic hypotension [OH], constipation, and erectile dysfunction), sleep disorders, and lower urinary tract symptoms (LUTS).[2]

Studies show that LUTS are prevalent in 27% to 61% of patients with PD, and these symptoms are more prevalent in patients with PD when compared to an age-matched healthy cohort.[3] These symptoms, which worsen as PD progresses, include storage symptoms (urinary urgency, frequency, and nocturia) and/or voiding symptoms (urinary hesitancy, weak stream, and urinary retention). Notably, nocturia defined as the need to wake up at night more than once to void appears to be one of the most prevalent urinary symptoms with an overall prevalence of 59% in patients with PD.[2,4,5]

Nocturia has an obvious impact on total sleep time, quality of sleep, and sleep efficiency.[6] Unfortunately, patients with PD experience a broad spectrum of sleep disorders such as insomnia, rapid eye movement (REM) sleep behavior disorder, and circadian rhythm disturbances, which may occur in 60% to 90% of these patients.[7,8] Although it has been well established that the prevalence of nocturia and sleep disorders is high in the PD population, it is poorly understood whether the nocturia drives sleep disorders or whether the sleep disorders allow opportunistic nocturia. We therefore aim to describe the intersectionality of sleep disorders and OAB/nocturia in patients with PD to maximize treatment strategies for OAB/nocturia in this particular population.

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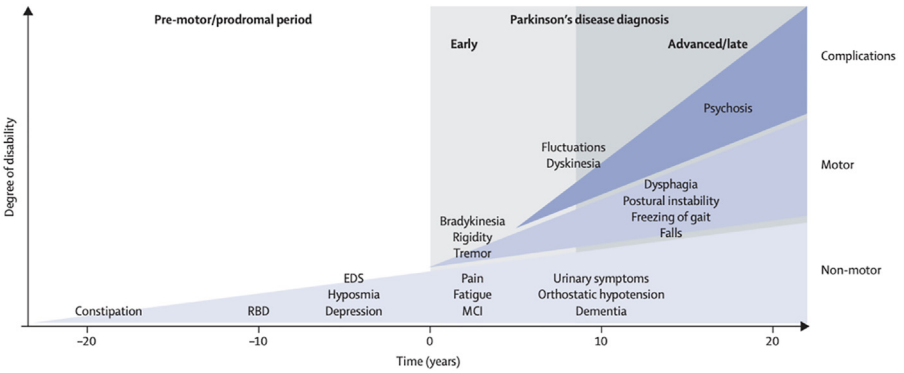

Fig. 1. Clinical symptoms and time course of PD progression. (*Reprinted* with permission from Elsevier. The Lancet, 2015 Aug 29;386(9996):896-912.)

PATHOPHYSIOLOGY OF OAB IN PD

Coordination of micturition requires an intricate interplay of the central and peripheral nervous system pathways with the bladder and urethra. Several of these pathways are disrupted in patients with PD. Normal voiding function involves the integration of sensory information, such as bladder fullness, which travels from the afferent fibers of the hypogastric, pelvic, and pudendal nerves up the spinal cord to the periaqueductal gray (PAG) in the midbrain. The PAG receives additional input like time, social situation, and emotions from the cortical regions such as the anterior cingulate gyrus and prefrontal cortex. Integration of bladder volume status with social context in the PAG will either promote urinary storage through inhibition of the pontine micturition complex or initiate the micturition reflex resulting in detrusor contraction with coordinated urethral sphincter relaxation. The micturition reflex is also affected by the nigrostriatal dopaminergic pathways. Stimulation of D1 receptors in the nigrostriatal dopaminergic pathway within the basal ganglia inhibits the micturition reflex while stimulation of D2 receptors does the opposite, but the overall dopinergic effect within the basal ganglia is to exert a tonic inhibitory effect on the micturition reflex.[1,9]

In PD, the degeneration of dopaminergic cells leads to the loss of dopamine-mediated inhibition on the micturition reflex. This often clinically manifests as OAB (urinary frequency, urgency, and urgency incontinence) and detrusor overactivity, which has been demonstrated in 67% of patients with PD on urodynamic testing.[10,11] Furthermore, patients with PD have been found to develop severe frontal cortex deficits over time.[1] Frontal cortex lesions in the anterior cingulate cortex and frontal gyri have been shown to produce detrusor overactivity.[12] Functional MRI studies have demonstrated significant frontal cortex activity during bladder distension and micturition in healthy volunteers suggesting its significance in the regulation of micturition.[13] Therefore, lesions in these areas may disrupt sensory integration and alter bladder perception, leading to frequent, smaller volume voids and reduced bladder capacity. Furthermore, the frontal cortex has a bidirectional relationship with sleep. Lesions in the frontal cortex can impair REM sleep and disrupt sleep–wake cycles, potentially leading to conditions like narcolepsy and excessive daytime sleepiness, which in turn adversely affect frontal executive functions, including the processing of bladder sensory information and the planning of micturition.[14]

PD also affects the external urethral sphincter muscles, causing "sphincteric bradykinesia," which is the delayed or reduced ability to contract the sphincter in response to an urge to void.[15] This phenomenon coupled with detrusor overactivity often seen in PD compromises the individual's capacity to delay urination and prevent involuntary urine leakage. Conversely, some patients with PD may not relax their urethral sphincter rapidly or sufficiently when voiding, which can be perceived as urinary hesitancy or incomplete emptying.[15] This is a distinct and separate phenomenon to detrusor external sphincter dyssynergia, which is commonly found in spinal cord injury patients but rarely found in patients with PD.

PATHOPHYSIOLOGY OF NOCTURIA IN PD

The bladder physiology changes of detrusor overactivity, decreased functional bladder capacity, and bladder hypersensitivity offer an explanation for the increased prevalence of nocturia in patients with PD, but the exact cause of nocturia in patients with PD is likely multifactorial. Other contributors to nocturia include nocturnal polyuria, cardiovascular dysautonomia, disruption of the circadian

rhythm, and sleep disorders. Nocturnal polyuria, defined by the International Continence Society (ICS) as greater than 33% of the entire daily (24 hours) voided volume occurring at night for the elderly, contributes to nocturia due to excessive production of urine and is highly prevalent in patients with PD.[5]

In patients with PD, the diminishment of postganglionic efferent sympathetic neurons in baroreceptors and the myocardium leads to an impairment in norepinephrine release and defective vasoconstriction during the transition from lying flat to standing upright, resulting in a neurogenic form of OH as well as supine hypertension.[16] OH, a sequelae of autonomic dysregulation, is present in 30% to 50% of patients with PD, and prevalence increases with disease duration and age.[17] Its association with nocturia lies in the body's compensatory mechanisms. When blood pressure drops due to OH, the body attempts to restore homeostasis through the release of antidiuretic hormone (ADH) and activating the renin-angiotensin-aldosterone system leading to sodium and water retention during the day. Once the individual lies down, increased renal blood flow due to the volume expansion leads to osmotic diuresis and consequently increased urine production.

Disruption of the circadian rhythm in PD also leads to excessive urine production. The circadian rhythm operates as the body's internal clock and dictates when individuals feel awake or sleepy based on external light cues. It is regulated by melatonin and arginine vasopressin (AVP) levels in response to day/night cycles. Under physiologic circumstances at night, melatonin levels rise to promote sleep while AVP levels rise to promote water reabsorption in the kidneys and thus reducing urine volume. In PD, neurodegenerative changes disturb the circadian rhythm, evident from prevalent sleep disorders and reduced melatonin levels in patients with PD.[18] This disturbance likely diminishes the nocturnal AVP surge, contributing to increased nighttime urine production and nocturia.

SLEEP DISTURBANCES AND NOCTURIA

Nocturia significantly impacts sleep quality in patients with PD, who often suffer from sleep disorders. A meta-analysis of polysomnographic findings of patients with PD compared to an age-matched cohort revealed that patients with PD consistently experience reduced total sleep time, sleep efficiency, sleep latency (time it takes to fall asleep), and total REM sleep compared.[19] Additionally, patients with PD with more than 2 episodes of nocturia are shown to worse sleep metrics than those with fewer episodes.[6] Insomnia is a prevalent issue in PD, affecting 27% to 80% of patients, manifesting as difficulties in either falling or staying asleep.[20] Additionally, patients with PD frequently experience REM sleep behavior disorder (RBD), where the usual muscle relaxation during REM sleep is absent, leading to patients physically acting out their dreams, which can range from simple limb twitches to more violent movements, potentially harming themselves or bed partners.[21] This disorder, present in 33% to 46% of patients with PD, can precede PD's motor symptoms.[22,23] Restless legs syndrome (RLS), affecting about 15% of patients with PD, causes uncomfortable leg sensations, particularly in the evening, disrupting sleep onset. RLS prevalence tends to increase with PD progression and treatment duration.[22] Other notable sleep disturbances include parasomnias, excessive daytime sleepiness and obstructive sleep apnea, which is not thought to be associated with PD.[20] Nocturia is generally assumed to be bothersome because the urge to urinate is the primary reason for patients to wake up. However, given nocturia and sleep disorders often coexist in patients with PD, that assumption is not always correct. Patients who are awake due to sleep disturbances may not necessarily urinate because of an urge, but "convenience void" since they are already awake. This distinction suggests that improving sleep disorders could be more effective than focusing solely on nocturia management. For patients with PD, nocturia could stem from 2 distinct causes: fluid overload due to orthostatic hypotension and sleep disturbances; however, currently, no studies have definitively determined whether nocturia is due to nocturnal polyuria or sleep disturbances, though such distinctions could be explored in future research with voiding diaries.

WHY IT MATTERS?

The complex interplay of OAB, nocturia, and sleep disturbances in patients with PD drastically impairs sleep resulting in a reduction on QoL.[20,24] A Finnish population-based study found that nocturnal voiding twice or more per night correlates with poorer health-related QoL.[25] Additionally, nocturia and sleep impairment in patients with PD have been correlated with anxiety and depression.[26,27] The frequent need for nighttime bathroom visits also raises fall risks, which is particularly concerning due to PD-related motor instability. Compared to healthy counterparts, patients with PD have a higher fall incidence (54% vs 18%) and those experiencing nocturia have an increased risk of hip fractures, independent

of age.[28,29] These sleep disruptions not only affect patients with PD but also extend to their bed partners, causing secondary sleep disorders.[30] Although underresearched, these secondary effects add to the emotional, physical, and financial burdens faced by caregivers of patients with PD.

WORKUP OF OAB AND NOCTURIA IN PD

History and Physical Examination

Often, PD is first diagnosed by a neurologist or internist, but some patients with undiagnosed PD may present to Urology clinic for assessment of their LUTS as the earliest sign of PD. A careful inventory of LUTS should be performed which can be categorized as storage symptoms or voiding symptoms. Patients with nocturia should be assessed as to whether they are woken up due to urinary urgency or are "convenience voiding." Other potential causes of LUTS should be assessed such as benign prostatic hyperplasia (BPH), obstructive sleep apnea (OSA), diabetes, and strokes. Functional impairment from the motor symptoms of PD, such as tremors, bradykinesia, or postural instability, and social situation and support should be carefully assessed. Patients with PD with severe mobility issues can have functional incontinence because it takes significantly longer to reach the toilet and undress. PD caregivers report a significant care burden so integrating their needs is critical to formulating a management plan that is acceptable and achievable to both parties.[30] Caregivers also provide valuable information about the patient's fluid intake and sleep patterns that may be unrecognized by patients. A detailed review of both PD-specific and other medications is essential, as these can affect bladder function. Evening fluid intake and consumption of caffeine or alcohol should be monitored as these can exacerbate symptoms.

A physical examination can aid in identifying the causes and severity of LUTS. Blood pressure measurements can reveal orthostatic hypotension. Skin excoriation of the urogenital area provides insight on severity of incontinence as well as degree of social support. During a digital rectal examination, not only can the prostate size be assessed but also a crude assessment of sphincteric bradykinesia can be performed by asking the patient to contract their anal sphincter with delays in anal sphincteric contraction being suggestive of bradykinesia. Overall mobility, hand dexterity, and cognition should be accessed as functional status often dictates symptom management strategies.

Diagnostic Tools

Voiding diaries allow objective quantification of OAB symptoms, fluid intake quantity and quality, and can be useful in initiating targeted behavioral modifications. They are crucial in the diagnosis of nocturia and nocturnal polyuria. A 3-day voiding diary has been found to provide reliable information without overburdening patients with excessive data collection.[31] Questionnaires such as the American Urological Association Symptom Index (AUA-SI) and Overactive Bladder Symptom Score have been used to objectively measure LUTS in patients with PD and can track symptom changes with each intervention. Urine analysis should be performed when evaluating OAB symptoms to rule out urinary tract infections. Low postvoid residuals (PVRs) can rule out overflow incontinence while elevated PVR can suggest detrusor underactivity or bladder outlet obstruction. Routine urodynamics are not necessary in patients with PD as there is minimal risk of upper tract deterioration.[32] Urodynamics can be helpful in evaluating concomitant BPH and OAB symptoms in male patients with PD or distinguishing stress urinary incontinence and OAB symptoms in female patients given full bladder cough stress test on pelvic examinations may be difficult to perform due to mobility issues. Urodynamic findings can be used to counsel patients with PD who seek more invasive therapy for OAB. A retrospective study of 390 patients with PD found detrusor overactivity with impaired contractility on urodynamics in 42% of patients, which may increase the risk of urinary retention in these patients who undergo bladder botulinum toxin (BTX) injections for OAB.[33]

MANAGEMENT OF OAB, NOCTURIA, AND CONSEQUENTLY SLEEP DISTURBANCES IN PD

The management of OAB and nocturia in patients with PD is challenging given these symptoms often do not exist in isolation, and there is a significant heterogeneity in PD severity and symptom presentation among patients. Therefore, addressing nocturia and OAB in patients with PD demands a diverse approach. Conservative measures such as behavioral modifications should always be considered first before progressing to medical or procedural interventions. Therapies targeted at maximizing sleep and PD-targeted therapies should also be considered. Collaboration with neurologists, physiotherapists, and sleep specialists is often necessary to optimize other aspects of PD such as sleep disturbances and motor symptoms, which have a cascading effect on LUTS. Such a comprehensive, team-based approach is paramount in

navigating the complexities of LUTS in PD and optimizing patient outcomes (Fig. 2).

Behavioral Management

Behavioral modifications play a pivotal role in managing nocturia and OAB in patients with PD. These include minimizing fluid intake, especially 4 hours before sleeping, limiting caffeine and alcohol, and encouraging plain water for hydration. In a prospective study, a 25% reduction in baseline fluid intake improved urinary frequency, urgency, and nocturia.[34] Implementing timed voiding schedules every 3 to 4 hours during the day and voiding immediately before bed can minimize urinary urgency and nocturia. Patients with PD may benefit from structured pelvic floor physical therapy (PFPT) as well. Two pilot studies demonstrated improvement in urgency incontinence, nocturia, and overall QoL in patients who underwent pelvic floor exercises with electromyography (EMG) biofeedback for at least 8 weeks.[35] PFPT has almost no adverse events but can be burdensome for caretakers who must accompany patients with PD to the sessions. For patients with dependent edema, compression stockings, and elevating legs in the afternoon can facilitate fluid redistribution and reduce nocturnal diuresis. Most diuretics take effect in 6 to 8 hours, so their intake in the late afternoon or evening should be avoided to prevent excessive nighttime urination.[24] External collection catheters (condom catheter, Purewick, Becton-Dickinson (BD)- Franklin Lakes, NJ) and bedside commodes can provide as alternatives for those who struggle to reach the bathroom in time and are a much safer alternative than a foley catheter.[36] Installing night-lights in pathways to the bathroom and removing floor obstacles such as rugs can reduce the risk of falls. Behavioral changes, such as minimizing daytime recumbency, sleeping with the head elevated at a 10° to 20° angle, and taking alpha-1 adrenoceptor agonists like midodrine, can effectively improve orthostatic hypotension, yet none of these interventions have been evaluated for their effectiveness in improving nocturia or OAB symptoms in patients with PD.[37] A study of 29 healthy volunteers noted a 146 mL decrease in nighttime voided volumes after 6 days of head up tilt sleeping.[38] Collectively, these behavioral and environmental modifications form an integrative strategy to manage nocturia and OAB while promoting both safety and sleep quality for patients with PD. Additionally, patients and their caregivers can greatly benefit from counseling on incontinence products and perineal skin care with barrier creams to help manage any incontinence.

Sleep-targeted Management

Improving the sleep quality in patients with PD can improve OAB and nocturia. General good sleep hygiene such as minimizing daytime naps (especially >20 minute naps), maintaining a consistent sleep schedule, reducing noise and light disturbances in the bedroom, and compliance with continuous positive airway pressure devices in those with OSA should be encouraged. With guidance from sleep specialists and neurologists, optimization of dopaminergic medication and sleep aids such as melatonin and antidepressants can improve sleep quality. Dopamine agonists have been shown to improve sleep parameters in multiple studies and appear especially effective for patients with PD with RLS.[23,39–41] Weaning off dopaminergic medication at night is theorized to

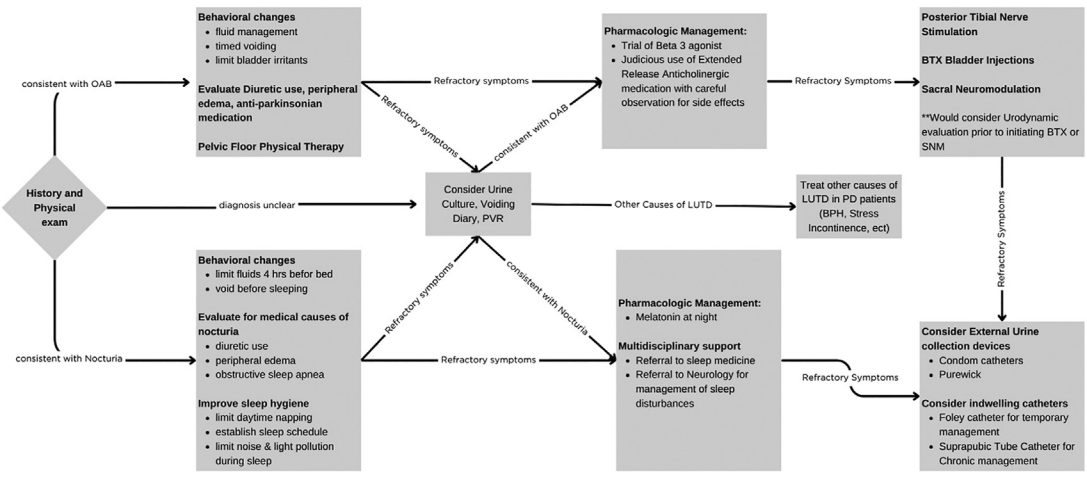

Fig. 2. Diagnosis and treatment algorithm for OAB and nocturia in patients with PD.

exacerbate insomnia as patients begin to notice the return of resting tremors and inability to get into comfortable positions in bed due to rigidity.[42] A study comparing extended-release levodopa versus placebo of 40 patients with PD demonstrated improvement in nocturnal akinesia and a trend toward increased total sleep time.[43] Extended-release levodopa at bedtime has also been reported to improve nocturia.[44] Varying doses of melatonin (1–12 mg) have been shown to be effective in improving nocturia with minimal side effects. A phase 2 study using 2 mg of sustained release melatonin in adults with PD demonstrated improvement in nighttime frequency of void from 3 to 1.67 after a 6 week period without any adverse events.[45] Other hypnotic medications such as trazodone, zolpidem, and clonazepam are effective at treating insomnia, RBD, and RLS, but the side-effect profile of these agents (dizziness, drowsiness, and cognitive impairments) suggests judicious use of these agents in patients with PD.[23] Given that melatonin is an over-the-counter supplement, the urologic provider can easily recommend this therapy.

Parkinson's Disease-targeted Therapy

Antiparkinsonian medication

The main classes of drugs used to treat the motor symptoms of PD include levodopa, dopamine agonist, and monamine oxidase type B (MAO-B) inhibitors. Treating the motor symptoms of PD has not been shown to improve OAB or nocturia, but these medications can impact LUTS. Therefore, it is important to be cognizant of the effects especially in patients who have recently started these medications. Urodynamics performed on 26 levodopa-naïve patients with PD 1 hour after the administration of levodopa demonstrated worsening detrusor overactivity and decrease bladder capacity (22% decrease).[46] However, after 2 months of levodopa therapy, repeat urodynamics on these patients demonstrated a delay in bladder sensation during filling, improvement in detrusor overactivity (93% improvement), and bladder capacity (33% improvement).[46] No randomized controlled trial (RCT) has evaluated the effects of dopamine agonist on LUTS, but one study suggested improvement in nocturia when patients with PD were switched from bromocriptine to pergolide and bladder capacity has been shown to increase in patients taking apomorphine.[47,48] Rasagiline, a second-generation MAO-B inhibitor, demonstrated an increase in bladder capacity by 16%, first desire to void by 34%, and decreased PVR by 53% when compared to placebo in patients with mild PD.[49] The effects of levodopa, dopamine agonist, and MAO-B inhibitors on LUTS are mixed and undefined due to dopamine's varied affinity for the D1 and D2 receptors as well as downregulation of dopamine receptors over time.

Deep Brain Stimulation

Deep brain stimulation (DBS) of the substantia nigra has been shown to significantly improve motor symptoms in patients with PD, but its efficacy in treating LUTS is mixed.[50] A study comparing DBS to oral PD medications or apomorphine pump showed DBS patients experienced less nocturia, but their overall LUTS were the same.[51] A study involving urodynamics performed on 16 patients with PD before and after their DBS was turned on demonstrated a delay in the initial desire to void (199 vs 135 mL) and increase in bladder capacity (302 vs 174 mL) with the DBS turned on.[52] A study compared DBS of the globus pallidus pars interna versus subthalamic nucleus (STN) showed urinary incontinence and frequency trended toward improvement in either DBS location but was only statistically significant in the STN group.[53] However, nocturia did not improve for either group.[53] A recent study on 416 patients with PD concluded similar results of improved urinary urgency, frequency, and incontinence without any changes in nocturia.[54]

Bladder-targeted Therapy

Anticholinergic medication

Anticholinergic medications have been the basis of treatment of OAB and neurogenic detrusor overactivity. However, their side-effect profile (dry eyes, dry mouth, constipation, and cognitive dysfunction) can compound PD symptoms, which limits their use and adherence to the medication. The cognitive dysfunction of anticholinergic OAB medication is of particular concern given it adds to the anticholinergic burden for patients with PD who are taking anticholinergic medication for antiparkinsonian therapy. Additionally, patients with PD are inherently at risk for early cognitive decline and dementia.

Few anticholinergic medications have been studied specifically in patients with PD. Oxybutynin was evaluated in 7 patients with PD who were noted to have decreased frequency, nocturia, and incontinence with unchanged PVR after 12 weeks of therapy.[55] Tolterodine has been shown to increase bladder capacity, decrease number of voids, and urgency episodes without increasing PVR.[56,57] However, 20% of patients with PD discontinued the medication due to constipation, dizziness/headache, and lack of improvement in symptoms. An RCT comparing

solifenacin (5–10 mg) to placebo in 23 patients with PD showed no significant improvement in mean number of voids per 24 hour period, but there was a significant decrease in urinary incontinence episodes from 1.3 to 0.5 episodes and nocturia (2.6–1.6 episodes over a 24 hour period) during the open label phase.[58] Side effects included constipation, xerostomia, and urinary retention, which resolved with the withdrawal of solifenacin. A recent RCT of fesoterodine (4 mg) versus placebo in 63 patients with PD demonstrated marginal decrease in voiding episodes in 24 hours (8.6 vs 7 episodes), nocturia (2.7 vs 2.3), and urgency incontinence episodes (1.8 vs 1.6).[59] Fesoterodine appears well tolerated as adverse events included xerostomia and constipation in 1 patient. There were no changes in baseline cognitive function or PVR after starting fesoterodine.[59] Although there is limited evidence to support the use of one anticholinergic over another in patients with PD, anticholinergics that do not cross the blood–brain barrier are generally recommended to minimize the potential cognitive side effects in patients at risk for cognitive impairment.[60] Given the marginal improvement of OAB/nocturia with anticholinergics in patients with PD and considering the substantial potential of these medications to worsen confusion and sleep–wake cycles in this group, we recommend the use of anticholinergics only if no other oral medication options are available and advise to use extended-release forms starting at the lowest possible dose.

Beta-3 agonist medication

Mirabegron and Vibegron are beta-3 agonists that have proven to be effective in managing idiopathic OAB. They offer an advantage over anticholinergic medications given their minimal side-effect profile, but their use can be limited by cost and lack of data on efficacy in PD. No RCT has been conducted on the efficacy and safety of beta-3 agonists in patients with PD. A retrospective study of 50 patients with PD started on 50 mg of mirabegron noted that 60% of the patients reported improvement or resolution of their OAB symptoms.[61] There was a statistically significant reduction of nocturia episodes. Only 2 adverse events were reported, which were dizziness and diaphoresis, which resolved after the medication was discontinued. However, compliance with mirabegron was reportedly low as only 46% of patients continued the medication after a median follow-up of 19 months. A prospective study of mirabegron 50 mg started in 30 patients with PD with OAB symptoms that have been refractory to anticholinergics demonstrated 80% of the patients reported improved incontinence QoL scores without any adverse events.[62] Overall, beta-3 agonists offer a much better safety profile compared to anticholinergic medication for OAB/nocturia in patients with PD while the efficacy is likely comparable.

Vasopressin

Desmopressin is a synthetic analog of ADH and has been proven to be effective for nocturnal polyuria. However, extreme caution should be taken with its use in patients with PD due to severe risk of hyponatremia, confusion, and orthostatic hypotension. A study using intranasal desmopressin for nocturia in 8 patients with PD showed a significant decrease in nocturia in 5 out of the 8 patients.[63] Adverse events include 1 patient who stopped the medication due to severe hyponatremia and confusion, which resolved after the withdrawal of desmopressin.

Botulinum toxin

For patients with PD who either are unable to tolerate the side effects or are poorly compliant with pharmacotherapy for OAB/nocturia, BTX injections into the bladder can be considered. Literatures supporting the use BTX injections into the bladder are based on 2 formulations of BTX, which are onabotulinumtoxinA (Botox) and abobotulinumtoxinA (Dysport).[24] The most recent and largest study of BTX injections in patients with PD included 24 patients (17 men and 7 women) who underwent 100 U of Botox for urinary incontinence.[64] Twenty-nine percent of patients reported complete resolution of the urgency urinary incontinence, while 79% of the patients reported improvement in their OAB symptoms 1 month after their first injection. Adverse events included 25% of patients who had a urinary tract infection and 12.5% of the patients did have to start clean intermittent catheterization for incomplete bladder emptying. Smaller studies using 100 U of Botox or 500 U of Dysport for OAB in patients with PD concluded similar improvement in bladder capacity, urinary frequency, and urgency incontinence, but also noted the risk of increase in PVR.[65,66] Interestingly, a prospective study of 10 patients with PD (4 female and 6 male) who underwent 200 U of Botox for OAB symptoms refractory to pharmacotherapy shared similar improvements with OAB symptoms without a statistically significant increase in PVR after a follow-up of 4 months.[67] No conclusive evidence exists regarding BTX efficacy in improving nocturia in patients with PD, due to underpowered studies and a lack of specific focus on nocturia as an outcome. However, studies in other populations with OAB suggest that BTX does not significantly reduce nocturia. Therefore, we would advise

against BTX for pure nocturia. When considering BTX bladder injections for patients with PD, it is crucial to assess baseline bladder contractility, PVR, and the potential for bladder outlet obstruction, particularly in males, due to the risk of urinary retention and challenges with self-catheterization if needed from limited hand dexterity. Additionally, Botox and Dysport are not interchangeable, and currently, there are no studies that directly compare their dose or efficacy in patients with PD. We would recommend any patient with PD undergo urodynamics prior to BTX injection to assess for risk of urinary retention and confirmation of diagnosis.

Neuromodulation

Several small studies have evaluated posterior tibial nerve stimulation (PTNS) and sacral neuromodulation (SNM) for patients with PD. A study of 47 patients with PD who underwent 12 weeks of PTNS demonstrated encouraging results with a mean decrease of daytime frequency episodes by 5.6 times and nocturia episodes by 2.7 times.[68] Other studies have supported these findings as well in addition to improvement in bladder capacity without any reported adverse events.[69] PTNS may improve OAB/nocturia symptoms acutely with almost no side effects, but the durability of the treatment remains unknown. Additionally, PTNS can be burdensome to patients due to the frequent clinic visits for the treatment, and implantable PTNS have not been studied in patients with PD. Very few studies have directly evaluated the use of SNM in patients with PD. A retrospective review of 34 patients with PD at a single institution who were evaluated for SNM with either peripheral nerve evaluation (7 patients) or stage 1 evaluation (27 patients) found that 82% of the patients proceeded to a permanent implant.[70] Of note, the indication for SNM in the majority of these patients was for refractory OAB symptoms (88%) while 12% of the patients were evaluated for nonobstructive urinary retention. Furthermore, 68% of the patients were able to discontinue their OAB medications after lead implantation. We do not routinely perform urodynamics in patients with PD who chose PTNS, but given the invasiveness of SNM, urodynamics is often performed before proceeding to ensure diagnostic accuracy.

Indwelling catheters

While several pharmacologic and procedural interventions exist to improve OAB and nocturia in patients with PD, these options may lose their efficacy over time given that PD is a progressive disease. Patients with severe OAB and nocturia that have been refractory to conservative measures or medications and/or unable to tolerate Botox, or neuromodulation, can consider indwelling catheters for severe incontinence management. It should be considered particularly when skin breakdown or hygiene becomes an issue or if their family can no longer manage the burden of the incontinence. Urethral Foley catheters can be considered acutely, but due to the risk of urethral erosion, long-term management is best with a suprapubic tubes (SPTs). The procedure has inherent risks, which include bowel injury, vascular injury at the time of placement, but special considerations for patients with PD include the risk of inadvertent tube dislodgment given the cognitive impairment, motor symptoms, and dementia associated with PD. Many patients and caregivers report high satisfaction with an SPT as the tube's location away from the urethra offers more freedom of movement and comfort during daily activities and sleep.[71]

SUMMARY

OAB and nocturia are highly prevalent in patients with PD due to bladder physiology alterations and sleep cycle disturbances that occur as the neurologic degenerative disease progresses. These symptoms severely affect the QoL both patients with PD and their bed partners. Management of these patients requires a careful assessment of their PD status, available support structure, and tailoring of therapy that is feasible and effective. Often, multiple interventions are required for success. Lastly, optimal management of these symptoms involves a coordinated effort from a multispecialty approach involving urologist, neurologist, sleep specialist, and pelvic floor specialist.

CLINICS CARE POINTS

- The pathophysiology of OAB and Nocturia in patients with PD is multifaceted.
- Managing sleep disturbances and OAB in patients with Parkinson's disease improves nocturia, overall QoL of the patient and their bed partners, and minmizes risk of falls.
- Melatonin is a low risk sleep aid that urologist can safely prescribe patients with PD with bothersome nocturia and sleep disturbances; however complex management of sleep disturbances in patients with PD should involve a sleep specialist.

DISCLOSURE

None.

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