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REVIEW

Perspectives on the urological care in Parkinson's disease patients

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Summary ***Parkinson's disease (PD) is recognized as the most common neurodegenerative disorder after Alzheimer's disease. Lower urinary tract symptoms are common in patients with PD, either storage symptoms (overactive bladder symptoms or OAB) or voiding symptoms. The most important diagnostic clues for urinary disturbances are provided by the patient's medical history. Urodynamic evaluation allows the determination of the underlying bladder disorder and may help in the treatment selection. Pharmacologic interventions especially anticholinergic medications are the first-line option for treating OAB in patients with PD. However, it is important to balance the therapeutic benefits of these drugs with their potential adverse effects. Intra-detrusor Botulinum toxin injections, electrical stimulation were also used to treat OAB in those patients with variable efficacy. Mirabegron is a β3-agonist that can also be used for OAB with superior tolerability to anticholinergics. Desmopressin is effective for the management of nocturnal polyuria which has been reported to be common in PD. Deep brain stimulation (DBS) surgery is effective in improving urinary functions in PD patients. Sexual dysfunction is also common in PD. Phosphodiesterase type 5 inhibitors are first-line therapies for PD-associated erectile dysfunction (ED). Treatment with apomorphine sublingually is another therapeutic option for PD patients with ED. Pathologic hypersexuality has occasionally been reported in patients with PD, linked to dopaminergic agonists. The first step of treatment of hypersexuality consists of reducing the dose of dopaminergic medication. This review summarizes the epidemiology, pathogenesis, risk factors, genetic, clinical manifestations, diagnostic test, and management of PD. Lastly, the urologic outcomes and therapies are reviewed.***

KEY WORDS: Parkinson's disease; Lower urinary tract dysfunction; Neurogenic bladder, Urology.

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INTRODUCTION

Parkinson's disease (PD) is the most common neurodegenerative movement disorder. In Europe, the prevalence and incidence rates for PD are estimated at approximately 108-257/100 000 and 11-19/100 000 per year, respectively (1). Although the cause of PD is unknown, the pathologic manifestation involves the loss or dysfunction of dopaminergic neurons in the substantia nigra pars compacta (2). The neuropathologic hallmark of PD is the presence of Lewy bodies composed mostly of alpha-synuclein and ubiquitin. It is believed that the occurrence of PD is due to a combination of genetic and environmental factors (3). The cardinal motor symptoms of PD are tremor, rigidity, bradykinesia/akinesia, and postural instability, but the clinical picture includes other motor and non-motor symptoms (4). A variety of non-motor symptoms are common in PD. They include disturbed autonomic function with orthostatic hypotension, constipation and urinary disturbances, a variety of sleep disorders and a spectrum of neuropsychiatric symptoms (5). Diagnosis of PD is based on history and examination. History can include prodromal features (rapid eye movement, sleep behavior disorder, hyposmia, constipation), characteristic movement difficulty (tremor, stiffness, slowness), and psychological or cognitive problems (cognitive decline, depression, anxiety). Examination typically demonstrates bradykinesia with tremor, rigidity, or both. Dopamine transporter single-photon emission computed tomography can improve the accuracy of diagnosis when the presence of parkinsonism is uncertain (6). Misdiagnoses between Parkinson's tremor and essential tremor are relatively common. Electrophysiological and functional imaging examinations can be useful in the distinction of the two, but both approaches suffer from some limitations (7). PD interferes with various aspects of quality of life, particularly those related to physical and social functioning (8).

The primary goal in the management of PD is to treat the symptomatic motor and nonmotor features of the disorder. Effective management should include a combination of nonpharmacological and pharmacological strategies to maximize clinical outcomes (9). Oral levodopa, the initial gold-standard therapy for PD, is still the most effective and widely used therapeutic option (10). In advanced PD, therapeutic interventions include device-aided therapies such as continuous subcutaneous apomorphine infusion, levodopa-carbidopa intestinal gel infusion, and deep brain stimulation (11). Supportive non-pharmaco-

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logical therapies are used in early and advanced PD patients. It should include physical rehabilitation, psychological support, occupational therapy, speech, language, and swallowing therapy, and nutrition (12).
Bladder dysfunctions are quite common in PD. They may occur at any stage of the illness and get worse with advancing and aggravating disease. The most prominent dysfunction is the so-called *overactive bladder* (OAB). The main clinical problem of PD patients consists in reduced inhibition with consequentially resulting overactivity of the detrusor muscle, meaning the urge to urinate in the absence of adequate bladder filling (13). The most common storage symptoms of patients with PD are nocturia, followed by frequency and urinary incontinence. Some patients presented functional obstructive symptoms. The most frequent obstructive symptom was incomplete emptying of the bladder (14). Obstructive symptoms may be secondary to anticholinergics, obstructive uropathy, or point to the presence of *multiple system atrophy* (MSA). Dysfunction of the striated urethral sphincter and pelvic musculature can be seen in variable numbers in PD (15). Antimuscarinic medications are the first-line treatment for OAB symptoms. Antimuscarininc drugs may exacerbate PD-related constipation and xerostomia, and caution is advised when using these medications in individuals where cognitive impairment is suspected. Desmopressin is effective for the management of nocturnal polyuria which has been reported to be common in PD. Intra-detrusor injections of botulinum toxin are effective therapy for detrusor overactivity, however, are associated with the risk of urinary retention (16). Subthalamic *deep brain stimulation* (DBS) has a significant and urodynamically recordable effect leading to a normalization of pathologically increased bladder sensibility (17). *Percutaneous tibial nerve stimulation* (PTNS) improves the urinary symptoms and urodynamic parameters in patients with PD (18).
Sexual dysfunction (SD) in PD, which has been suggested as a result of central and autonomic dysfunction compounded by defective motor skills, reduced self-esteem, and comorbid psychiatric states like anxiety and depression (19). The prevalence of SD is reported high in male patients (65%), but much lower in female patients (36%). There are different types of SD: *erectile dysfunction* (ED) and loss of ejaculation control in male patients, and much lower self-esteem in female patients (20). Optimal dopaminergic treatment should facilitate sexual encounters of the couple. Appropriate counseling diminishes some of the problems (reluctance to engage in sex, problems with ejaculation, lubrication, and urinary incontinence). Treatment of ED with sildenafil and apomorphine is evidence-based (21). We performed a narrative review to briefly discuss the epidemiology, pathogenesis, risk factors, genetic contribution, clinical course, diagnosis, and treatment of PD. The urologist had an important role in the management of urologic manifestations of patients with PD. We reviewed the current literature regarding the urological outcomes and management of patients with PD.

Materials and methods

We searched electronic databases including *PubMed*, the Scopus database for published studies that analyzed the role of the following *Medical Subject Headings* terms: '*Parkinson's disease*' (AND) '*Management*' (AND) '*Diagnosis*' (AND) '*epidemiology*' (AND) '*genetic contribution*' (AND) '*risk factor*' (OR) '*Parkinson's disease*' (AND) '*urologic dysfunction*' (AND) '*Management*' (OR) '*Parkinson's disease*' (AND) '*Erectile dysfunction*' (AND) '*Management*'.
This was done to ensure the comprehensive inclusion of articles related to neurogenic bladder in PD patients. The initial search resulted in 350 articles. After review, we initially excluded papers that were not relevant (72). At the completion of the review, articles were selected based on their clinical relevance related to the aim. When all duplicates are thrown out, a total of 90 papers were used to extract necessary information.

Overview of PD

Epidemiology of PD

PD affects 1-2 per 1000 of the population at any time. PD prevalence is increasing with age, it affects 1% of the population above 60 years (22). The median age of onset is 60 years; the mean duration of the disease from diagnosis to death is 15 years. Male sex is recognized as a prominent risk factor in developing PD. Both incidence and prevalence of PD are 1.5 to 2.0 times higher in men than in women. Age at onset is 2.1 years later in women (53.4 years) than in men (51.3 years) (23).
The overall prevalence of PD appears to be lower in Eastern studies compared to Western ones. In a meta-analysis of 39 European studies until 2004, the authors reported a prevalence rate of 108-257/100,000 when considering only high-quality studies that utilized a standard diagnostic criterion (24).

Pathogenesis of PD

The main pathological features of PD are the loss of dopaminergic neurons with subsequent depigmentation of the substantia nigra pars compacta and the presence of Lewy bodies (25).
Lesions initially occur in the dorsal motor nucleus of the glossopharyngeal and vagal nerves and anterior olfactory nucleus. Thereafter, less vulnerable nuclear grays and cortical areas gradually become affected (26).
The spinal cord lesions may contribute to clinical symptoms (pain, constipation, poor balance, lower urinary tract complaints, and sexual dysfunction) that occur during the premotor and motor phases of sporadic PD (27).
PD does not fulfill key criteria to be diagnosed as prionopathy. Nonetheless, abnormal forms of α-synuclein seem to propagate in the brain of PD patients.
The finding of Lewy bodies and α-synuclein deposits in nigral fetal neurons transplanted over a decade earlier into the striatum could support the existence of a prion-like pathogen as the cause of PD (28).

Risk factors of PD

Significant predictors of PD emerged (in order of strength): pesticide use, family history of neurologic disease, and history of depression. The predicted probability of PD was 92.3% (odds ratio = 12.0) with all three predictors positive (29). Other potential risk factors include

Table 1.
Motor and non-motor symptoms of Parkinson's disease.

Motor symptoms	Non motor symptomse
· Tremor	· **Neuropsychiatric problems:** cognitive impairment, depression, anhedonia, apathy, anxiety, panic attacks, delirium, hallucinations, illusions
· Rigidity	· Sleep problems
· Bradykinesia, akinesia	· Oily skin, dandruff
· Loss of balance	· Sensory impairment
· Speech and facial expression difficulties	· **Urinary disturbances:** Urgency, frequency, urge incontinence, nocturia, sexual dysfunction
· Gait disturbance	· **Gastrointestinal disturbances:** Drooling, dyspepsia, constipation, abdominal pain, fecal incontinence
· Impaired handwriting and grip force	· Blood pressure variations with orthostatic hypotension and tachycardia
	· Fatigue

environmental toxins, drugs, brain microtrauma, focal cerebrovascular damage, and genomic defects (30). There is an association between anemia experienced early in life and the later development of PD (31). Exposure to toxins in the environment has been linked to PD-associated neurodegeneration particularly heavy metals, pesticides, and illicit drugs (32). Some infectious diseases such as mumps, scarlet fever, influenza, whooping cough, and herpes simplex infections may play a role in the development of PD (33).

Genetic contribution to PD

A-synuclein (SNCA) was the first PD gene identified in a large Italian-American family (the Contursi kindred) with autosomal dominant inheritance (34). A total of 18 PD loci have been nominated through linkage analysis (PARK1-15) or genome wide association studies (PARK16-18).
Mutations within the genes at 6 of these loci (SNCA, LRRK2, PRKN, DJ1, PINK1, and ATP13A2) have conclusively been demonstrated to cause familial parkinsonism. In addition, common polymorphisms within 2 of these same genes (SNCA and LRRK2) and variation in 2 other genes not assigned to a PARK locus (MAPT and GBA) are now well-validated risk factors for PD (35).

Clinical Features of PD

PD comprises a range of motor and non-motor features (Table 1).
The presence of bradykinesia, rest tremor, rigidity, and loss of postural reflexes are the most commonly identified motor symptoms of PD, although other clinical features can also be identified during disease progressions, such as bulbar dysfunction, neuro-ophthalmological abnormalities, and respiratory disturbances (36). Most non-motor symptoms are not fully levodopa-responsive and are suggested to manifest extra-nigral pathology. These symptoms include autonomic, sleep, sensory, and neuropsychiatric symptoms (37).

Diagnosis of PD

The *Movement Disorder Society* (MDS) clinical diagnostic criteria for PD mentioned that the first essential criterion is parkinsonism, which is defined as bradykinesia, in combination with at least 1 of rest tremor or rigidity. Once parkinsonism has been diagnosed, the diagnosis of clinically established PD requires absence of absolute exclusion criteria, at least two supportive criteria, and no red flags (38). Those criteria and red flags are summarized in Table 2. Early falls, poor response to levodopa, symmetry of motor manifestations, lack of tremor, and early autonomic dysfunction are probably useful in distinguishing other parkinsonian syndromes from PD. The levodopa or apomorphine challenge and olfactory testing are probably useful in distinguishing PD from other parkinsonian syndromes (39).
Structural MRI is useful to differentiate PD from secondary and atypical forms of parkinsonism. 123I-ioflupane *single-photon emission computed tomography* (SPECT) is a valid tool in the differential diagnosis between PD and non-degenerative tremors. Cardiac 123I-metaiodobenzylguanindine SPECT and 18F-FDG *positron emission tomography* (PET) have the potential to differentiate PD from atypical parkinsonism (40).

Differential diagnosis

Although the most common cause of parkinsonism is PD, the differential diagnosis includes many other causes of parkinsonism. Aside from drug-induced parkinsonism, related to drug-induced changes in the basal ganglia motor circuit secondary to dopaminergic receptor blockade, the most common mimickers of PD are parkinsonian syndromes, such as MSA and progressive supranuclear palsy, *dementia with Lewy bodies* (DLB), *vascular parkinsonism* (VP), a parkinsonian syndrome that is associated with cerebrovascular disease (41).

Management of PD

There are several drugs available to treat motor impairments in PD. First, drugs that increase brain levels of dopamine such as Levodopa are used. In addition, drugs that mimic dopamine were used such as dopamine agonists. Lastly, drugs that inhibit dopamine breakdown has been used. MAO-B inhibitors can inhibit the activity of monoamine oxidase B. Usually, MOA-B inhibitors reduce the symptoms of PD. Selegiline or deprenyl is one of the inhibitors of MOA-B that is very active against PD along with levodopa. Tolcapone also reduces the requirement of levodopa to patients but it can induce severe hepatotoxicity. There are two types of *catechol-O-methyl transferase* (COMT) inhibitors being entacapone and tolcapone. COMT inhibitors are used to reduce the dose of levodopa (42). In most patients with PD, motor fluctuations and dyskinesias are relatively mild and can be adequately managed by adjustment of the oral medication. However, for patients experiencing disabling motor fluctuations and dyskinesias despite optimized medical therapy, device-assisted therapies should be considered (43).

Table 2.
Parkinson's disease diagnostic criteria of the movement disorder society.

Movement disorder society criteria (53)	
Supportive criteria	· Clear and dramatic beneficial response to dopaminergic therapy. · Presence of levodopa-induced dyskinesia · Rest tremor of a limb, documented on clinical examination (in past, or on current examination) · The presence of either olfactory loss or cardiac sympathetic denervation on MIBG scintigraphy
Absolute exclusion criteria	· Unequivocal cerebellar abnormalities, such as cerebellar gait, limb ataxia, or cerebellar oculomotor abnormalities · Downward vertical supranuclear gaze palsy, or selective slowing of downward vertical saccades · Diagnosis of probable behavioral variant frontotemporal dementia or primary progressive aphasia, defined according to consensus criteria within the first 5 y of disease · Parkinsonian features restricted to the lower limbs for more than 3 y · Treatment with a dopamine receptor blocker or a dopamine-depleting agent in a dose and time-course consistent with drug-induced parkinsonism · Absence of observable response to high-dose levodopa despite at least moderate severity of disease · Unequivocal cortical sensory loss, clear limb ideomotor apraxia, or progressive aphasia · Normal functional neuroimaging of the presynaptic dopaminergic system · Documentation of an alternative condition known to produce parkinsonism and plausibly connected to the patient's symptoms, or, the expert evaluating physician, based on the full diagnostic assessment feels that an alternative syndrome is more likely than Parkinson's disease
Red flags	· Rapid progression of gait impairment requiring regular use of wheelchair within 5 y of onset · A complete absence of progression of motor symptoms or signs over 5 or more y unless stability is related to treatment · Early bulbar dysfunction: severe dysphonia or dysarthria or severe dysphagia (requiring soft food, nasogastric tube, or gastrostomy feeding) within first 5 y · Inspiratory respiratory dysfunction: either diurnal or nocturnal inspiratory stridor or frequent inspiratory sighs · Severe autonomic failure in the first 5 y of disease. · Recurrent (> 1/y) falls because of impaired balance within 3 y of onset · Disproportionate anterocollis (dystonic) or contractures of hand or feet within the first 10 y · Absence of any of the common non-motor features of disease despite 5 y disease duration. These include sleep dysfunction (sleep-maintenance insomnia, excessive daytime somnolence, symptoms of REM sleep behavior disorder), autonomic dysfunction (constipation, daytime urinary urgency, symptomatic orthostasis), hyposmia, or psychiatric dysfunction (depression, anxiety, or hallucinations) · Otherwise-unexplained pyramidal tract signs, defined as pyramidal weakness or clear pathologic hyperreflexia (excluding mild reflex asymmetry and isolated extensor plantar response) · Bilateral symmetric parkinsonism.

Many experimental studies are going to test the applications of antibodies to target and degrade extracellular α-synuclein molecules. Passive and active immunization techniques against α-synuclein have been shown to convey neuroprotective effects in animal models (44).

Urologic outcomes of PD

Prevalence of urologic symptoms among the PD population

Seventy-four percent of patients with early-to-moderate disease report more than one bladder disturbance symptom. Severe bladder symptoms are reported in 27-39% of PD patients. Both storage and voiding symptoms are highly prevalent in patients with PD. More than 50% of patients have OAB symptoms (45). The severity of the neurological disease is correlated with the occurrence of voiding dysfunction, these findings corroborate the results of other studies which showed that *lower urinary tract symptoms* (LUTS) increase accordingly with PD progression (46).

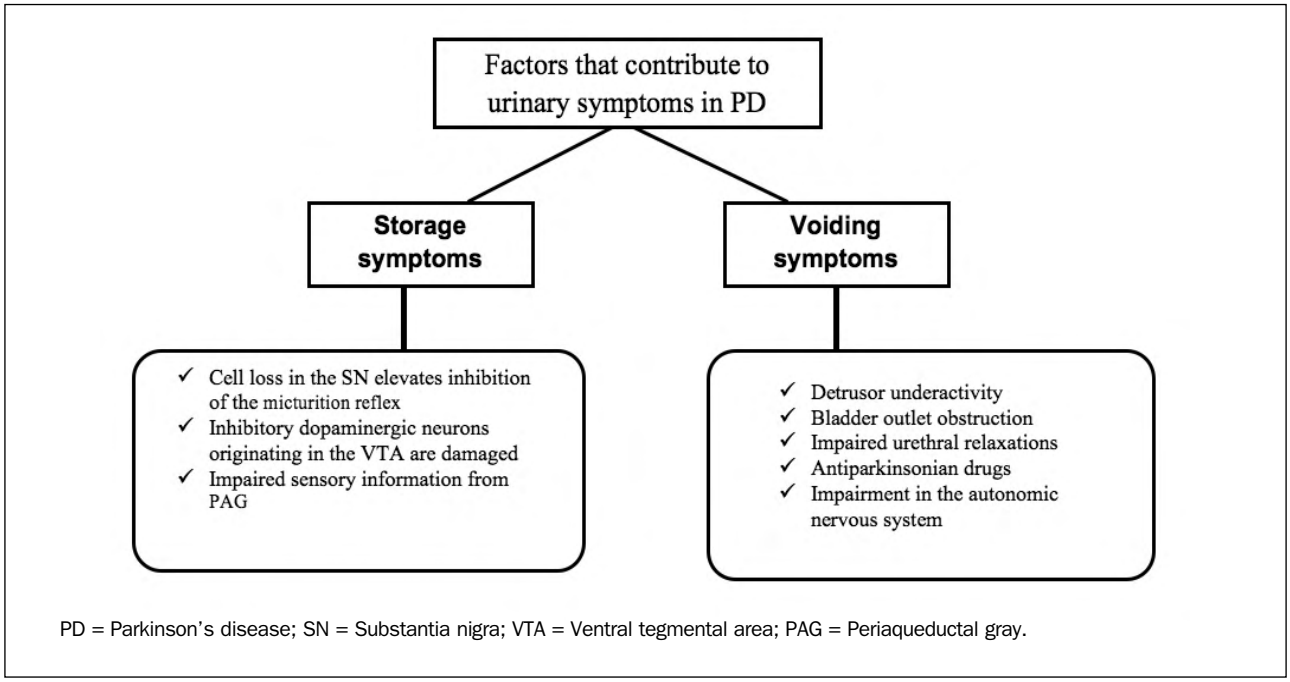
Urologic clinical symptoms

The pattern and mechanism of storage symptoms have been partly clarified as the hypothesis most widely proposed is that the basal ganglia output has an overall inhibitory effect on the micturition reflex in healthy individuals, and with cell loss in the substantia nigra, detrusor overactivity develops through an inability to activate the dopamine D1 receptor-mediated tonic inhibition. A parallel mechanism may be that in PD, the inhibitory dopaminergic neurons originating in the substantia nigra may be more damaged than the stimulatory dopaminergic neurons originating in the ventral tegmental area, thereby inducing urgency and frequency. Impaired sensory information from periaqueductal gray could also contribute to storage symptoms (47). However, those of voiding disorders have yet to be elucidated, and there have been only a few reports that dopa-responsive detrusor under-activity or impaired urethral relaxations exist, and *post-void residual* urine (PVR) does not occur frequently. These findings suggest that early and untreated PD patients also have not only storage disorders but also mainly subclinical voiding disorders (48).

Detrusor underactivity or bladder outlet obstruction (BOO) underlie the mechanism of voiding symptoms in patients with PD. PD patients mostly maintain an acceptable voiding efficiency and low PVR volume. In the meantime, PD mostly affects the elderly, overlapping the age group with high morbidity of *benign prostatic hyperplasia* (BPH). Neurogenic BOO in PD patients still draws less attention (49). *Detrusor sphincter dyssynergia* (DSD) is a rare cause of voiding dysfunction in PD. DSD was observed on voiding at a rate of 0-3% (50). Underactive bladder in up to 50 % of patients with PD.

The mechanism of detrusor weakness in PD remains unclear and warrants further exploration (51). A study suggested that a weak detrusor in PD might have a central origin. It is necessary to follow PVR carefully in PD patients with advanced gait disorder because PVR might

Figure 1.
Suggested mechanisms responsible for urinary symptoms in patients with PD.



PD = Parkinson's disease; SN = Substantia nigra; VTA = Ventral tegmental area; PAG = Periaqueductal gray.

increase in such patients (52). Obstructive symptoms might possibly result from treatment with particular antiparkinsonian drugs. Also, it should be noted that Lewy bodies can be seen in several types of neurons, including central and peripheral components of the autonomic nervous system, in advanced PD. Thus, obstructive symptoms in patients with PD might result from micturition hyporeflexia due to impairment in the autonomic nervous system (53). The mechanisms responsible for urinary symptoms in PD patients are summarized in Figure 1.

Neurogenic lower urinary dysfunction (NLUD) can induce anxiety and depression in patients. A study was implemented by *Benli et al.* to investigate whether NLUD, which is frequently seen in PD, has an effect on the development of anxiety and depression in these patients. The study included 32 males (66.6%) and 16 females (33.3%); in total 48 subjects were registered. It was concluded that the incidence of NLUD, anxiety and, depression was increased in PD. In addition, NLUD was found to be a risk factor for the development of anxiety and depression (54).

Clinical scales

The scale for outcomes in PD for autonomic symptoms (SCOPA-AUT) is a specific scale to assess autonomic dysfunction in PD patients. It includes six urinary items that assess both storage and voiding phases. SCOPA-AUT is an acceptable, consistent, reliable, and valid scale (55). The *International Prostate Symptom Score* (IPSS) has been used both in men and women for patients with neurological diseases; several teams used it in PD patients, including in advanced stage, and after DBS. *Overactive Bladder Symptom Score* (OABSS) has been used to evaluate urinary symptoms in PD patients but it needs further validation (56).

Findings on urodynamic studies

The urodynamic examination is recommended for male PD patients with voiding dysfunction. It can show detrusor hyperreflexia associated with BOO or detrusor dysfunction with BOO (57).

Urodynamic findings could differentiate patients with MSA from those with PD. Patients with MSA showed lower maximal flow rate, larger PVR with decreased compliance, and impaired contractility, whereas patients with PD had a higher incidence of detrusor overactivity and associated leakage (58).

A study conducted by *Vurture et al.* strongly suggests that a vast majority of OAB symptoms in patients with PD can be attributed to DO on urodynamics (97.1%).

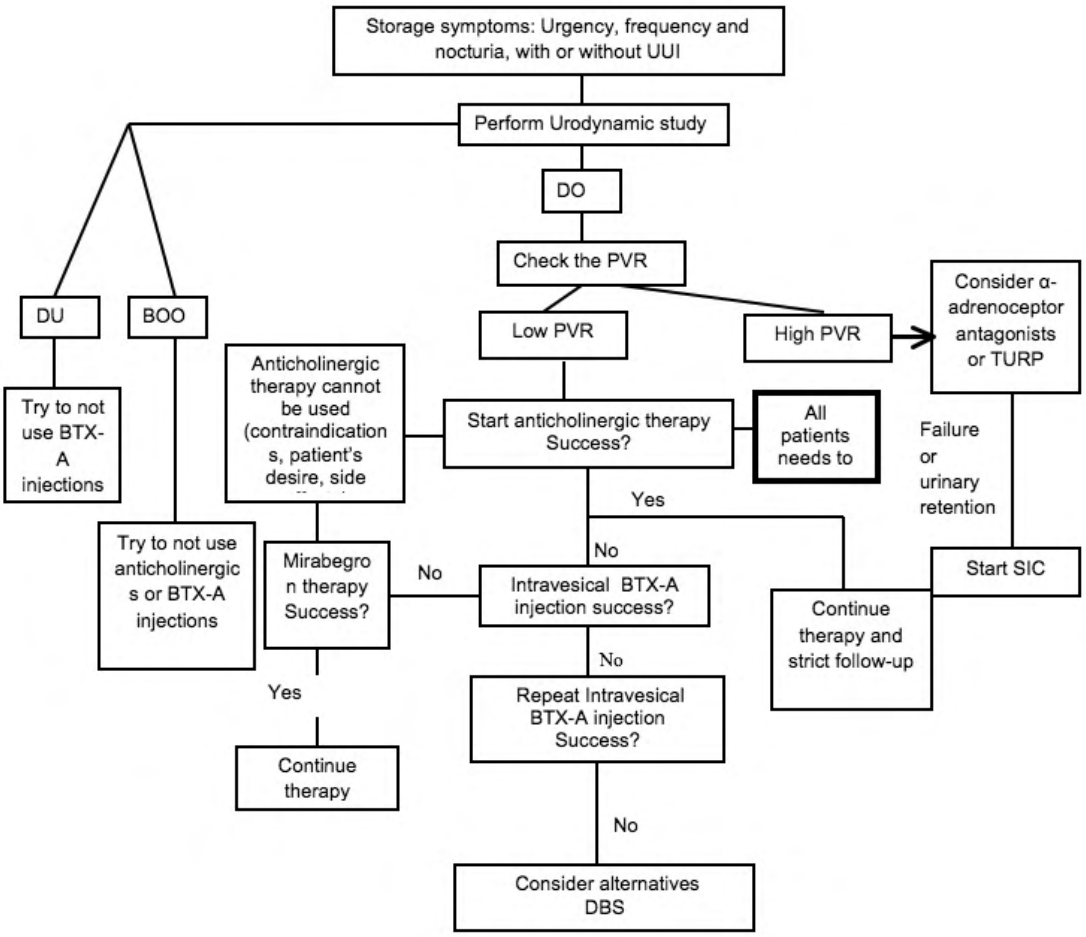
However, the high rates of other abnormalities such as BOO (36.8%), detrusor underactivity (47%), and increased PVR (16.7%) suggest that neurogenic DO is not the only contributor of OAB symptoms in patients with PD (59).

Special focus on nocturia in PD

Nocturia is a common non-motor symptom in PD but has been poorly studied. Nocturia may manifest as a result of reduced functional bladder capacity or nocturnal polyuria; however, most often the cause is multifactorial. Disorders of circadian rhythm regulation are known to occur with sleep disturbances in PD that may also contribute to nocturia (60).

The bladder diary provides a prospective real-time assessment of bladder symptoms, which is cost-effective and relatively straightforward for patients to complete. It provides a more accurate assessment of night-time frequency and voided nocturnal urine volumes. A bladder diary is an essential tool in the assessment of nocturia in patients with PD (61).

Figure 2.
Algorithm for the management of storage symptoms in PD patients.



PD = Parkinson's disease; DO = Detrusor overactivity; DU = Detrusor underactivity; BOO = Bladder outlet obstruction; UUI = Urge urinary incontinence; SIC = Self-intermittent catheterization; PVR = Post void residual volume; BTX-A = Botulinum toxin A; TURP = Transurethral resection of the prostate; DBS = Deep brain stimulation.

Urologic Management of PD

Management of the storage symptoms (OAB symptoms) in PD patients

A detailed algorithm for the management of the storage symptoms in PD patients is summarized in Figure 2.

General measures and physical treatment

Behavioral therapy included pelvic floor muscle exercises, bladder training, fluid and constipation management. Providers should consider behavioral therapy as an initial treatment for urinary symptoms in PD. It was demonstrated in a small study conducted by *Vaughan et al.* (62). A study was implemented by *McDonald et al.* to assess the feasibility and efficacy of *bladder training* (BT) for troublesome LUTS in PD. Thirty-eight participants were randomized (18 to *conservative advice* (CA), 20 to BT groups). Both CA and BT were associated with significant improvements in volume voided, number of micturitions, symptom severity scores, and measures of quality of life (all $p < 0.05$). At 12 weeks, compared to CA, BT was associated with significant superiority on patient perception of improvement ($p = 0.001$). At 20 weeks, BT remained associated with greater improvement in interference in daily life (63).

Dopaminergic therapy

It is uncertain whether L-dopa medication can improve micturition disorders. Some have reported that L-dopa improves micturition symptoms, but others have reported conflicting results. In addition, the effects of L-dopa on bladder function are unknown (64). The acute mixed stimulation of D1 and D2 receptors by apomorphine has been reported to reduce bladder outflow resistance. In contrast, acute dopaminergic stimulation by L-dopa challenge has been reported to worsen detrusor overactivity and to reduce bladder capacity in patients with PD. However, the worsening effect of acute L-dopa administration conflicts with the clinical experience of bladder function improvement reported by PD during L-dopa therapy (65). These findings suggest that the effects of dopaminergic treatment on bladder control are very different, according to their

receptorial activity, producing a cumulative effect of a multidrug daily treatment difficult to predict. Combined, balanced activation of D1/D2 receptors could be beneficial for treating urinary symptoms caused by detrusor hyperreflexia in PD as demonstrated *Brusa et al.* They conducted an open-label study where extended-release levodopa at bedtime showed significant improvement of OAB symptoms, specifically nocturia (66). *Winge et al.* concluded in their trial that dopaminergic therapy relieves cognitive executive dysfunction, as it seems to improve functional bladder control in those of their patients, who benefit from medication during their storage phase (67).

Antimuscarinic drugs

Antimuscarinic agents are the first-line treatment for OAB symptoms. These include oxybutynin, tolterodine, solifenacin, darifenacin, fesoterodine, and trospium chloride. Only Solifenacin had a class of evidence (level 1a) for urinary dysfunction in PD (16). The central effects of these medications may result in alterations in cognition and consciousness in susceptible individuals. caution needs to be used in elderly patients with preexisting dementia (68). A randomized-controlled trial (RCT) that assesses the use of solifenacin succinate for OAB in PD was done by *Zesiewicz et al.* Patients were randomized to receive solifenacin succinate 5-10 mg daily or placebo for 12 weeks followed by an 8-week open-label extension. Twenty-three patients were randomized in the study. There was no significant improvement in the primary outcome measure in the double-blind phase, but there was an improvement in the number of micturitions per 24 h period in the solifenacin succinate group compared to placebo at a mean dose of 6 mg/day ($p = 0.01$). In the open-label phase, the mean number of urinary incontinence episodes per 24 h period decreased ($p = 0.03$), as did the number of nocturia episodes per 24 h period ($p = 0.01$) (69). *Yonguc et al.* conducted an RCT to test the use of fesoterodine fumarate for OAB in PD. From May 2016 to May 2018, 63 patients were randomized to receive fesoterodine 4 mg or placebo for 4 weeks. At the end of 4 weeks of the randomization phase, patients have received fesoterodine fumarate 4 mg daily for another 4 weeks at the open-label extension phase. OAB symptoms were significantly improved in older adults with PD under fesoterodine fumarate treatment, and this advantage continued in the open-label portion in the short term (70).

Mirabegron

Mirabegron is an orally active, β3-adrenoceptor agonist approved for the treatment of OAB. The main theoretical advantage of β3-adrenoceptor agonists for the treatment of OAB is that they lack the typical side effects of antimuscarinics. There are only a few trials that test the efficacy of mirabegron in PD patients. *Peyronnet et al.* conducted a study that aimed to assess the outcomes of mirabegron for the treatment of OAB symptoms in patients with PD. Fifty patients (mean 74 years old) were included. Before being treated with mirabegron, 56% had failed prior anticholinergic therapy. After 6 weeks of mirabegron 50 mg, five patients (11.4%) had a complete resolution of their OAB symptoms; 25 patients (50%) reported improvement, 23 (46%) reported no change, and 2 (4%) reported worsening of their OAB symptoms. The number of pads per day decreased from 1.5 to 0.9 ($p = 0.01$) and so did the number of nocturia episodes (from 3 to 2.6/night; $p = 0.02$). Mirabegron has an excellent safety profile in their trial (71). *Gubbiotti et al.* concluded in their pilot study that mirabegron is a safe and effective treatment in patients with PD and OAB refractory to anticholinergics in the short-term follow-up (72). In another RCT conducted by *Cho et al.*, it was concluded that mirabegron was effective in treating OAB symptoms in patients with parkinsonism with acceptable adverse events (73).

Botulinum toxin therapy

There are limited data on the efficacy of intravesical *botulinum toxin* (BT) injection in PD patients. *Kulaksizoglu et al.* implemented a trial to evaluate the efficacy of intravesical BT injection for OAB symptoms in patients with PD. Sixteen patients were followed for 12 months. Intradetrusor injection technique with 30-point template was employed. All patients received 500 international units of botulinum toxin-A. The follow-up was at week one and every 12 weeks thereafter for 12 months. The initial mean functional bladder capacity was 198.6 +/- 33.7 mL. At 3-month follow-up the mean bladder capacity increased to 319 +/- 41.1 mL. The quality of life assessment of the primary caregiver as well as the patients also statistically improved after the injections. No central nervous system side effects were noted (74). *Vurture et al.* conducted a study to test the outcomes of intradetrusor onabotulinum toxin A (BoNT-A) injection in patients with PD. All PD patients who underwent intradetrusor injections of BoNT-A for storage symptoms between 2010 and 2017 were included in their retrospective study. A 100 U dose of BoNT-A was used for the first injection in all patients. Out of 24 patients analyzed, 19 reported improvements of their OAB symptoms 4 weeks after the first injection (79.2%) with complete resolution of urgency urinary incontinence in seven patients (29.1%; $p < 0.001$). Three of the patients had to start *clean intermittent catheterization* (CIC) after the first injection (12.5%) (75). Some authors hypothesize that BoNTA might be better tailored to "OAB wet"/motor urgency (59). Intravesical BoNT-A might not be a good indication in patients with *detrusor hyperactivity and impaired contractility* (DHIC) and high PVR (76). It was mentioned in the *International Continence Society* (ICS) guidelines that intravesical BT injection is a promising method to treat intractable detrusor overactivity in PD. Also, guidelines state that it is important to differentiate MSA from PD before completing botulinum injections. But there was no recommendation for dosages, risk factors for retention or difficulty voiding or long-term effectiveness are available (77).

Sacral neuromodulation

Sacral neuromodulation (SNM) is an effective therapy that should be considered among the treatment options for PD patients with OAB symptoms. Urodynamic parameters associated with obstruction may be predictive of SNM failure in PD patients and may help guide patient selection (78). Few studies have been performed to determine the effects of *percutaneous posterior tibial nerve stimulation* (PTNS) on neurogenic DO in patients, especially, with PD.

Kabay et al. conducted a trial to investigate the effect of PTNS treatment after 12 weeks on urodynamic and clinical findings in patients with PD with neurogenic DO. A total of 47 patients with PD with neurogenic DO were enrolled in the study. Their results have demonstrated that PTNS improves the lower urinary tract symptoms and urodynamic parameters in patients with PD (79).
Transcutaneous tibial nerve home stimulation can be used in clinical practice as an effective nonpharmacological resource for the reduction of OAB symptoms in women with PD (80).

Deep brain stimulation
Deep brain stimulation (DBS) has been used as a surgical treatment for motor symptoms in advanced PD. An exploratory post hoc analysis was performed of specific LUTS items of questionnaires used in an RCT with 128 patients (NSTAPS study). Urinary incontinence and frequency improved after both *globus pallidus pars interna* (GPi) DBS and the *subthalamic nucleus* (STN) DBS at 12 months postoperatively, but this was only statistically significant for the STN DBS group (P = 0.004). The improvements after DBS were present in both men (p = 0.01) and women (p = 0.05). Nocturia and urinary incontinence did not improve significantly after any type of DBS, irrespective of sex (81). DBS is associated with increased bladder capacity and volume triggering bladder contraction, increased time to first desire to void. While DBS appears to be a promising therapy for modulating LUTS in PD patients, the current research is mostly limited to small cohorts. Larger clinical trials are needed to truly delineate how DBS affects urinary disturbances (82).

Management of the voiding symptoms in PD patients
Concern has existed about the risks of incontinence with *transurethral resection of the prostate* (TURP) in PD patients with BOO. *Roth et al.* investigated the outcome of TURP in patients with a secure neurological diagnosis of PD.
A total of 23 patients with PD who underwent TURP for benign prostatic obstruction were evaluated retrospectively. It was concluded that TURP for benign prostatic obstruction in patients with PD may be successful in up to 70% and the risk of de novo urinary incontinence seems minimal (83). One of the greatest areas of concern for many patients considering TURP is the possibility of incontinence or inability to void despite surgical intervention. *Tyson et al.* demonstrated in their study that the use of the temporary prostatic urethral stent provided a good provocative test that enabled patients to experience what their voiding status would be if they were to undergo definitive surgical management (84).
Doxazosin resulted in the improvement of LUTS and the maximum flow rate and was well tolerated in men with PD. The response to treatment is dependent on the severity of neurological disability (85). Recently the α1 adrenergic receptor antagonist terazosin was shown to activate PGK1, a possible target for the mitochondrial deficits in PD related to its function as the initial enzyme in ATP synthesis during glycolysis. It has been shown that terazosin had neuroprotective effects in neurotoxin models of nigrostriatal degeneration in invertebrates and rodents, including after delayed administration. Additionally, terazosin reduced α-synuclein levels in transgenic mice and neurons derived from patients with LRRK2 mutation-associated (44). An epidemiologic study was performed by *Sasane et al.* to test the PD occurrence rate in 113,450 individuals from the United States with 5 or more years of follow-up. Patients were classified as tamsulosin users (n = 45,380), terazosin/alfuzosin/doxazosin users (n = 22,690), or controls matched for age, sex, and Charlson comorbidity index score (n = 45,380). Terazosin/alfuzosin/doxazosin users did not differ in PD risk from matched controls (P = 0.29) but rather that tamsulosin may in some way potentiate PD progression (86). In case of significant and symptomatic PVR, a specific treatment is necessary in order to empty the bladder. The gold standard therapy in PD patients with neurogenic bladder still the self-intermittent-catheterizations (87).

Managing Nocturia in PD
Managing nocturia in PD patients necessitates managing reduced functional bladder capacity and nocturnal polyuria. The use of antimuscarinics, detrusor injection of BT, neuromodulation, and CIC could be useful to manage reduced bladder capacity. Desmopressin and late-afternoon diuretic could help in the management of nocturnal polyuria (60).

Managing incontinence in PD
In a systemic review of 3 studies with a total sample size of n = 1077, 25 percent of the women with PD suffer from urgency incontinence compared to seven percent of the women without Parkinson's disease (p < 0.01). Men with PD were affected with a 28% rate in comparison of 6% of men without Parkinson's disease (p < 0.01). With pelvic floor muscle exercises and accompanying measures as well as with injections of botulinum toxin A a reduction of urinary incontinence seems to be possible (88). Artificial urinary sphincter implantation shows significantly worse continence rates for patients with PD, even though it is considered as a safe procedure (89).

Management of the sexual dysfunction in PD patients
Impulse control disorders (ICDs) affect up to 40% of patients with PD using dopamine agonists and about 15% of patients with PD overall. The mainstay of medical management for ICD is reducing or discontinuing dopamine agonists. Cognitive-behavioral therapy was found to be useful for the treatment of ICD in patients with PD (90). Sildenafil citrate may be considered to treat ED in patients with PD as concluded in multiple studies. The benefit of apomorphine on sexual function in some patients suggests a possible role in the treatment of impotence in PD but its role is not validated. A daily dose of transdermal testosterone gel improved testosterone deficiency symptoms in men with PD (91). Pergolide substantially improved sexual function in the younger male patients who were still interested in sexual activities (92).

Conclusions
Urinary symptoms and sexual dysfunctions are common in PD patients, occurring in any stage of the disease. PD patients experience both storage and voiding difficulties.

Storage symptoms, specifically OAB are markedly common in those patients. Anticholinergics and mirabegron remain potential treatment options. DBS, intradetrusor botulinum toxin injections can be used to treat intractable OAB symptoms in PD. TURP could be performed safely in PD patients with BPH if MSA is excluded. Other supportive non-pharmacological therapies such as behavioral therapy are used in early and advanced PD patients. Phosphodiesterase-5 inhibitors are essential to treat sexual dysfunction. Treatment of all urologic dysfunction in PD is optimal with a multidisciplinary approach to improve the quality of life of these patients.

References

1. Balestrino R, Schapira AHV. Parkinson disease. Eur J Neurol. 2020; 27:27-42.

2. Lew M. Overview of Parkinson's disease. Pharmacotherapy. 2007; 27:155S-160S.

3. Béné R, Antic S, Budisic M, et al. Parkinson's disease. Acta Clin Croat. 2009; 48:377-80.

4. Balestrino R, Schapira AHV. Parkinson disease. Eur J Neurol. 2020; 27:27-42.

5. Sveinbjornsdottir S. The clinical symptoms of Parkinson's disease. J Neurochem. 2016; 139 (Suppl 1):318-324.

6. Armstrong MJ, Okun MS. Diagnosis and treatment of Parkinson disease: A review. JAMA. 2020; 323:548-560.

7. Baumann CR. Epidemiology, diagnosis and differential diagnosis in Parkinson's disease tremor. Parkinsonism Relat Disord. 2012; 18 (Suppl 1): S90-2.

8. Schrag A, Jahanshahi M, Quinn N. How does Parkinson's disease affect quality of life? A comparison with quality of life in the general population. Mov Disord. 2000; 15:1112-8.

9. DeMaagd G, Philip A. Parkinson's disease and its management: Part 1: disease entity, risk factors, pathophysiology, clinical presentation, and diagnosis. P T. 2015; 40:504-32.

10. Pirtošek Z, Bajenaru O, Kovács N, et al. Update on the management of Parkinson's disease for general neurologists. Parkinsons Dis. 2020 ; 2020:9131474.

11. Marsili L, Bologna M, Miyasaki JM, Colosimo C. Parkinson's disease advanced therapies . A systematic review: More unanswered questions than guidance. Parkinsonism Relat Disord. 2021; 83:132-139.

12. Witt K, Kalbe E, Erasmi R, Ebersbach G. Nichtmedikamentöse Therapieverfahren beim Morbus Parkinson [Nonpharmacological treatment procedures for Parkinson's disease]. Nervenarzt. 2017; 88:383-390. [Article in German].

13. Jost WH. Urological problems in Parkinson's disease: clinical aspects. J Neural Transm (Vienna). 2013; 120:587-91.

14. Campos-Sousa RN, Quagliato E, da Silva BB, et al. Urinary symptoms in Parkinson's disease: prevalence and associated factors. Arq Neuropsiquiatr. 2003; 61:359-63.

15. Singer C. Urinary dysfunction in Parkinson's disease. Clin Neurosci. 1998; 5:78-86..

16. Batla A, Tayim N, Pakzad M, Panicker JN. Treatment options for urogenital dysfunction in Parkinson's disease. Curr Treat Options Neurol. 2016; 18:45.

17. Seif C, Herzog J, van der Horst C, et al. Effect of subthalamic deep brain stimulation on the function of the urinary bladder. Ann Neurol. 2004; 55:118-20.

18. Kabay S, Canbaz Kabay S, Cetiner M, et al. The clinical and urodynamic results of percutaneous posterior tibial nerve stimulation on neurogenic detrusor overactivity in patients with Parkinson's Disease. Urology. 2016; 87:76-81.

19. Celikel E, Ozel-Kizil ET, Akbostanci MC, Cevik A. Assessment of sexual dysfunction in patients with Parkinson's disease: a case-control study. Eur J Neurol. 2008; 15:1168-1172.

20. Meco G, Rubino A, Caravona N, Valente M. Sexual dysfunction in Parkinson's disease. Parkinsonism Relat Disord. 2008; 14:451-6.

21. Bronner G, Vodušek DB. Management of sexual dysfunction in Parkinson's disease. Ther Adv Neurol Disord. 2011; 4:375-83.

22. Tysnes OB, Storstein A. Epidemiology of Parkinson's disease. J Neural Transm 2017; 124:901-905.

23. Lee A, Gilbert RM. Epidemiology of Parkinson disease. Neurol Clin. 2016; 34:955-965.

24. Abbas MM, Xu Z, Tan LCS. Epidemiology of Parkinson's disease-East versus West. Mov Disord Clin Pract. 2017; 5:14-28.

25. Priyadarshi A, Khuder SA, Schaub EA, Priyadarshi SS. Environmental risk factors and Parkinson's disease: a metaanalysis. Environ Res. 2001; 86:122-7.

26. Liu CC, Li CY, Lee PC, Sun Y. Variations in incidence and prevalence of Parkinson's disease in Taiwan: a population-based nationwide study. Parkinsons Dis. 2016; 2016:8756359.

27. Del Tredici K, Braak H. Spinal cord lesions in sporadic Parkinson's disease. Acta Neuropathol. 2012; 124:643-64.

28. Linazasoro G. Pathogenesis of PD: missing the point. Mov Disord. 2010; 25:122-3.

29. Hubble JP, Cao T, Hassanein RE, et al. Risk factors for Parkinson's disease. Neurology. 1993; 43:1693-7.

30. Emamzadeh FN, Surguchov A. Parkinson's disease: biomarkers, treatment, and risk factors. Front Neurosci. 2018; 12:612.

31. Savica R, Grossardt BR, Carlin JM, et al. Anemia or low hemoglobin levels preceding Parkinson disease: a case-control study. Neurology. 2009; 73:1381-7.

32. Ball N, Teo WP, Chandra S, Chapman J. Parkinson's disease and the environment. Front Neurol. 2019; 10:218.

33. Vlajinac H, Dzoljic E, Maksimovic J, et al. Infections as a risk factor for Parkinson's disease: a case-control study. Int J Neurosci. 2013; 123:329-32.

34. Polymeropoulos MH, Lavedan C, Leroy E, et al. Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. Science. 1997; 276:2045-7.

35. Bekris LM, Mata IF, Zabetian CP. The genetics of Parkinson disease. J Geriatr Psychiatry Neurol. 2010; 23:228-42.

36. Váradi C. Clinical features of Parkinson's disease: the evolution of critical symptoms. Biology 2020; 9:103.

37. Wolters ECh. Non-motor extranigral signs and symptoms in Parkinson's disease. Parkinsonism Relat Disord. 2009 ; 15 (Suppl 3):S6-12.

38. Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord. 2015; 30:1591-601.

39. Suchowersky O, Reich S, Perlmutter J, et al. Quality Standards Subcommittee of the American Academy of Neurology. Practice

Parameter: diagnosis and prognosis of new onset Parkinson disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2006; 66:968-75.

40. Pagano G, Niccolini F, Politis M. Imaging in Parkinson's disease. Clin Med. 2016; 16:371-5.

41. Caproni S, Colosimo C. Diagnosis and differential diagnosis of Parkinson disease. Clin Geriatr Med. 2020; 36:13-24.

42. Jagadeesan AJ, Murugesan R, Vimala Devi S, et al. Current trends in etiology, prognosis and therapeutic aspects of Parkinson's disease: a review. Acta Biomed. 2017; 88:249-262.

43. Hayes MW, Fung VS, Kimber TE, O'Sullivan JD. Updates and advances in the treatment of Parkinson disease. Med J Aust. 2019; 211:277-283.

44. Stoker TB, Barker RA. Recent developments in the treatment of Parkinson's Disease. F1000 Res. 2020; 9:F1000 Faculty Rev-862.

45. Winge K, Nielsen KK. Bladder dysfunction in advanced Parkinson's disease. Neurourol Urodyn. 2012; 31:1279-83.

46. Sammour ZM, Gomes CM, Barbosa ER, et al. Voiding dysfunction in patients with Parkinson's disease: impact of neurological impairment and clinical parameters. Neurourol Urodyn. 2009; 28:510-5.

47. Winge K, Fowler CJ. Bladder dysfunction in Parkinsonism: mechanisms, prevalence, symptoms, and management. Mov Disord. 2006; 21:737-45.

48. Uchiyama T, Sakakibara R, Yamamoto T, et al. Urinary dysfunction in early and untreated Parkinson's disease. J Neurol Neurosurg Psychiatry. 2011; 82:1382-6.

49. Xing T, Ma J, Ou T. Evaluation of neurogenic bladder outlet obstruction mimicking sphincter bradykinesia in male patients with Parkinson's disease. BMC Neurol. 2021; 21:125.

50. Yeo L, Singh R, Gundeti M, et al. Urinary tract dysfunction in Parkinson's disease: a review. Int Urol Nephrol. 2012; 44:415-24.

51. Liu Z, Uchiyama T, Sakakibara R, Yamamoto T. Underactive and overactive bladders are related to motor function and quality of life in Parkinson's disease. Int Urol Nephrol. 2015 ; 47:751-7.

52. Terayama K, Sakakibara R, Ogawa A, et al. Weak detrusor contractility correlates with motor disorders in Parkinson's disease. Mov Disord. 2012; 27:1775-80.

53. Araki I, Kuno S. Assessment of voiding dysfunction in Parkinson's disease by the international prostate symptom score. J Neurol Neurosurg Psychiatry. 2000; 68:429-33.

54. Benli E, Ozer FF, Helvacı Yılmaz N, et al. Effect of bladder dysfunction on development of depression and anxiety in Parkinson's disease. Arch Ital Urol Androl. 2021; 93:336-340.

55. Forjaz MJ, Ayala A, Rodriguez-Blazquez C, et al. Assessing autonomic symptoms of Parkinson's disease with the SCOPA-AUT: a new perspective from Rasch analysis. Eur J Neurol. 2010; 17:273-9.

56. Pavy-Le Traon A, Cotterill N, et al. Clinical rating scales for urinary symptoms in Parkinson disease: critique and recommendations. Mov Disord Clin Pract. 2018; 5:479-491.

57. Xue P, Wang T, Zong H, Zhang Y. Urodynamic analysis and treatment of male Parkinson's disease patients with voiding dysfunction. Chin Med J 2014; 127:878-81.

58. Shin JH, Park KW, Heo KO, et al. Urodynamic study for distinguishing multiple system atrophy from Parkinson disease. Neurology. 2019; 93:e946-e953.

59. Vurture G, Peyronnet B, Palma JA, et al. Urodynamic mechanisms underlying overactive bladder symptoms in patients with Parkinson disease. Int Neurourol J. 2019; 23:211-218.

60. Batla A, Phé V, De Min L, Panicker JN. Nocturia in Parkinson's disease: why does it occur and how to manage? Mov Disord Clin Pract. 2016; 3:443-451.

61. Smith M, Seth J, Batla A, et al. Nocturia in patients with Parkinson's disease. Mov Disord Clin Pract. 2015; 3:168-172.

62. Vaughan CP, Burgio KL, Goode PS, et al. Behavioral therapy for urinary symptoms in Parkinson's disease: A randomized clinical trial. Neurourol Urodyn. 2019; 38:1737-1744.

63. McDonald C, Rees J, Winge K, et al. Bladder training for urinary tract symptoms in Parkinson disease: A randomized controlled trial. Neurology. 2020; 94:e1427-e1433.

64. Zhang LM, Zhang XP. Investigation of Urination Disorder in Parkinson's disease. Chin Med J. 2015; 128:2906-12.

65. Brusa L, Petta F, Pisani A, et al. Acute vs chronic effects of l-dopa on bladder function in patients mild Parkinson disease. Neurology. 2007; 68:1455-9.

66. Brusa L, Ponzo V, Stefani A, et al. Extended release levodopa at bedtime as a treatment for nocturiain Parkinson's disease: An open label study. J Neurol Sci. 2020; 410:116625.

67. Winge K, Werdelin LM, Nielsen KK, Stimpel H. Effects of dopaminergic treatment on bladder function in Parkinson's disease. Neurourol Urodyn. 2004; 23:689-96.

68. Pagoria D, O'Connor RC, Guralnick ML. Antimuscarinic drugs: review of the cognitive impact when used to treat overactive bladder in elderly patients. Curr Urol Rep. 2011; 12:351-7.

69. Zesiewicz TA, Evatt M, Vaughan CP, et al. Randomized, controlled pilot trial of solifenacin succinate for overactive bladder in Parkinson's disease. Parkinsonism Relat Disord. 2015; 21:514-20.

70. Yonguc T, Sefik E, Inci I, et al. Randomized, controlled trial of fesoterodine fumarate for overactive bladder in Parkinson's disease. World J Urol. 2020; 38:2013-2019.

71. Peyronnet B, Vurture G, Palma JA, et al. Mirabegron in patients with Parkinson disease and overactive bladder symptoms: A retrospective cohort. Parkinsonism Relat Disord. 2018; 57:22-26.

72. Gubbiotti M, Conte A, Di Stasi SM, et al. Feasibility of mirabegron in the treatment of overactive bladder in patients affected by Parkinson's disease: A pilot study. Ther Adv Neurol Disord. 2019; 12:1756286419843458.

73. Cho SY, Jeong SJ, Lee S, et al. Mirabegron for treatment of overactive bladder symptoms in patients with Parkinson's disease: A double-blind, randomized placebo-controlled trial (Parkinson's Disease Overactive bladder Mirabegron, PaDoMi Study). Neurourol Urodyn. 2021; 40:286-294.

74. Kulaksizoglu H, Parman Y. Use of botulinim toxin-A for the treatment of overactive bladder symptoms in patients with Parkinsons's disease. Parkinsonism Relat Disord. 2010; 16:531-4.

75. Vurture G, Peyronnet B, Feigin A, et al. Outcomes of intradetrusor onabotulinum toxin A injection in patients with Parkinson's disease. Neurourol Urodyn. 2018; 37:2669-2677.

76-Wang CC, Lee CL, Kuo HC. Efficacy and Safety of Intravesical OnabotulinumtoxinA Injection in Patients with Detrusor Hyperactivity and Impaired Contractility. Toxins. 2016; 8:82.

77. Sakakibara R, Panicker J, Finazzi-Agro E, et al. Parkinson's Disease Subcomittee, The Neurourology Promotion Committee in

The International Continence Society. A guideline for the management of bladder dysfunction in Parkinson's disease and other gait disorders. Neurourol Urodyn. 2016; 35:551-63.

78. Greenberg DR, Sohlberg EM, Zhang CA, et al. Sacral nerve stimulation in Parkinson's disease patients with overactive bladder symptoms. Urology. 2020; 144:99-105.

79. Kabay S, Canbaz Kabay S, Cetiner M, et al. The clinical and urodynamic results of percutaneous posterior tibial nerve stimulation on neurogenic detrusor overactivity in patients with Parkinson's Disease. Urology. 2016; 87:76-81.

80. Araujo TG, Schmidt AP, Sanches PRS, et al. Transcutaneous tibial nerve home stimulation for overactive bladder in women with Parkinson's disease: A randomized clinical trial. Neurourol Urodyn. 2021; 40:538-548.

81. Witte LP, Odekerken VJJ, Boel JA, et al. NSTAPS study group. Does deep brain stimulation improve lower urinary tract symptoms in Parkinson's disease? Neurourol Urodyn. 2018; 37:354-359.

82. Tabakin AL, Tunuguntla HSGR. Does deep brain stimulation improve Parkinson's disease-related lower urinary tract symptoms and voiding dysfunction? Bladder. 2021; 8:e46.

83. Roth B, Studer UE, Fowler CJ, Kessler TM. Benign prostatic obstruction and parkinson's disease--should transurethral resection of the prostate be avoided? J Urol. 2009; 181:2209-13.

84. Tyson MD, Hurd KJ, Nunez RN, et al. Temporary prostatic urethral stenting as a provocative tool to determine surgical eligibility in complex bladder outlet obstructed patients: our initial experience. Curr Urol. 2012; 6:82-6.

85. Gomes CM, Sammour ZM, Bessa Junior Jd, et al. Neurological status predicts response to alpha-blockers in men with voiding dysfunction and Parkinson's disease. Clinics 2014; 69:817-22.

86. Sasane R, Bartels A, Field M, et al. Parkinson disease among patients treated for benign prostatic hyperplasia with 1 adrenergic receptor antagonists. J Clin Invest. 2021; 131:e145112.

87. Savard E, Declemy A, Coindreau V, et al. Auto-sondages intermittents et rétentions urinaires des syndromes parkinsoniens [Self-intermittent-catheterization and urinary retentions in Parkinsonian syndromes]. Prog Urol. 2018; 28:987-992. [Article in French].

88. Siegl E, Lassen B, Saxer S. Inkontinenz--ein häufiges Problem für Menschen mit einer Parkinsonerkrankung. Eine systematische Literaturübersicht [Incontinence--a common issue for people with Parkinson's disease. A systematic literature review]. Pflege Z. 2013; 66:540-4. [Article in German].

89. Maurer V, Stahlberg J, Schiffmann I, et al. Continence and complication rates of artificial urinary sphincter devices (AMS 800) for Parkinson and stroke patients with incontinence after prostate surgery: retrospective analysis of a prospective database. Urol Int. 2021; 105:225-231.

90. Margolesky J, Betté S, Singer C. Management of urologic and sexual dysfunction in Parkinson disease. Clin Geriatr Med. 2020; 36:69-80.

91. Moussa M, Papatsoris AG, Abou Chakra M, et al. Erectile dysfunction in common neurological conditions: A narrative review. Arch Ital Urol Androl. 2020; 92:371-385

92. Pohanka M, Kanovský P, Bares M, et al. Pergolide mesylate can improve sexual dysfunction in patients with Parkinson's disease: the results of an open, prospective, 6-month follow-up. Eur J Neurol. 2004; 11:483-8.

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