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A Guideline for the Management of Bladder Dysfunction in Parkinson's Disease and Other Gait Disorders

Ryuji Sakakibara,[1]* Jalesh Panicker,[2] Enrico Finazzi-Agro,[3] Valerio Iacovelli,[4] Homero Bruschini,[5] and The Parkinson's Disease Subcomittee, The Neurourology Promotion Committee in The International Continence Society

[1]*Neurology, Internal Medicine, Sakura Medical Center, Toho University, Sakura, Japan*
[2]*Neurology, National Hospital for Neurology & Neurosurgery, London, United Kingdom*
[3]*Department of Experimental Medicine and Surgery, Tor Vergata University and Unit for Functional Urology, Policlinico Tor Vergata University Hospital, Rome, Italy*
[4]*School of Specialization in Urology, Tor Vergata University Unit for Functional Urology, Policlinico Tor Vergata University Hospital, Rome, Italy*
[5]*Urology, University of Sao Paulo, Brazil*

Parkinson's disease (PD) is a common neurodegenerative disorder, and lower urinary tract (LUT) dysfunction is one of the most common autonomic disorders with an estimated incidence rate of 27–80%. Studies have shown that bladder dysfunction significantly influences quality-of-life (QOL) measures, early institutionalisation, and health economics. We review the pathophysiology of bladder dysfunction in PD, lower urinary tract symptoms (LUTS), objective assessment, and treatment options. In patients with PD, disruption of the dopamine D1-GABAergic direct pathway may lead to LUTS. Overactive bladder (OAB) is the most common LUT symptom in PD patients, and an objective assessment using urodynamics commonly shows detrusor overactivity (DO) in these patients. The post-void residual (PVR) volume is minimal in PD, which differs significantly from multiple system atrophy (MSA) patients who have a more progressive disease that leads to urinary retention. However, subclinical detrusor weakness during voiding may also occur in PD. Regarding bladder management, there are no large, double-blind, prospective studies in this area. It is well recognised that dopaminergic drugs can improve or worsen LUTS in PD patients. Therefore, an add-on therapy with anticholinergics is required. Beta-3 adrenergic agonists are a potential treatment option because there are little to no central cognitive events. Newer interventions, such as deep brain stimulation (DBS), are expected to improve bladder dysfunction in PD. Botulinum toxin injections can be used to treat intractable urinary incontinence in PD. Transurethral resection of the prostate gland (TURP) for comorbid BPH in PD is now recognised to be not contraindicated if MSA is excluded. Collaboration of urologists with neurologists is highly recommended to maximise a patients' bladder-associated QOL. *Neurourol. Urodynam. 35:551–563, 2016.* © 2015 Wiley Periodicals, Inc.

Key words: guideline; management; oveactive bladder; Parkinson's disease; quality of life

INTRODUCTION

Parkinson's disease (PD) is a common movement disorder (tremor at rest, rigidity, and gait difficulty) associated with the degeneration of dopaminergic neurons in the substantia nigra. PD is the second most common degenerative neurological disease (the most common is Alzheimer's disease). Elderly gait disorders are often accompanied by bladder disorders; however, the exact reason behind this association is not clear. A potential explanation is that both the bladder and gait disorders originate from the same brain lesions that involve the prefrontal/mediofrontal area and basal ganglia neural circuit. Gait disorders in elderly subjects are typically Parkinsonian in nature. A brief differential diagnosis of elderly gait disorders from a urological viewpoint is discussed at the end of this report (Appendix 2). In addition to gait problems, patients with PD often show non-motor symptoms, including neuropsychiatric disorders, sleep disorders, sensory symptoms, and autonomic disorders.[1] Bladder dysfunction is one of the most common autonomic disorders in PD.[2,3] Studies have shown that bladder dysfunction significantly influences quality-of-life (QOL) measures, early institutionalisation, and health economics.[4,5] Unlike motor disorders, bladder dysfunction is non-responsive to levodopa, a precursor of central dopamine, suggesting this dysfunction occurs through a complex pathophysiology.[6] Indeed, the pathology of PD is not confined to the degeneration of dopaminergic neurons in the substantia nigra but rather involves multiple brain regions and neurotransmitters. To maximise patients' bladder QOL, add-on therapy for ameliorating dopamine-independent bladder dysfunction is necessary. In this guideline (a guideline for the management of bladder dysfunction in PD and other gait disorders), we critically review the neural control of micturition relevant to PD, pathophysiology of bladder dysfunction in PD (including objective assessment), and treatment options, including drugs and deep brain stimulation. A brief management strategy for bladder dysfunction in PD is discussed at the end of the report (Appendix 1).

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The Neurourology Promotion Committee in The International Continence Society consists of following authors: Helmut Madesbacher, Emmanuel Chartier Kastler, Waleed Altaweel, Marcio Averbeck, Melissa Davies, Jerzy Gajewski, Pablo Gomery, Thomas Kessler, Limin Liao, Andrei Manu-Marin, and Brigitte Schurch.
*Correspondence to: Ryuji Sakakibara, Neurology, Internal Medicine, Sakura Medical Center, Toho University, 5641 Shimoshizu, Sakura, 2858741 Japan.
E-mail: sakakibara@sakura.med.toho-u.ac.jp
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METHODOLOGY

Among various brain diseases, PD is one of the most extensively-studied areas in terms of bladder physiology. However, there have been no double-blind, controlled studies on bladder management. Using Medline (PubMed), Cochrane Reviews & other literature sources, more than 500 papers were extensively reviewed based on a defined set of keywords: Parkinson's disease (PD) and bladder, urinary sphincter, pelvic floor, lower urinary tract, urinary, incontinence, nocturia, toileting, and micturition. To determine how bladder disorders relate to elderly gait disorders, we identified 162 relevant papers, after excluding citation overlap. The search returned 51 papers on the neural control of micturition, 33 papers on bladder dysfunction in PD, 50 papers on lower urinary tract symprtoms (LUTS) and PD—drugs relationships and deep brain stimulation, 28 papers on the treatment of bladder dysfunction in PD and other treatments, and 22 papers used for Appendices 1 and 2, including flow charts. In terms of bladder management, the majority of the literature was at a level of evidence II-3 (evidence obtained from multiple time series designs with or without the intervention). Dramatic results in uncontrolled trials might also be regarded as this type of evidence. In addition, the literature often reported a recommendation grade B (at least fair scientific evidence suggests that the benefits of the clinical service outweighs the potential risks; thus, clinicians should discuss the service with eligible patients) or C (at least fair scientific evidence suggests that there are benefits provided by the clinical service, but the balance between benefits and risks are too close for making general recommendations; thus, clinicians need not offer it unless there are individual considerations). These results highlight the lack of double-blinded, controlled studies on the bladder management of PD patients, which is in contrast to previous published guidelines on bladder management in patients with spinal cord injury, multiple sclerosis, etc. Nevertheless, our report is the first step to expand the practical and scientific management of bladder dysfunction in patients with PD.

NEURAL CONTROL OF MICTURITION RELEVANT TO PD

Normal Micturition Circuit

The lower urinary tract (LUT) consists of two major components, including the bladder and urethra. The bladder has abundant muscarinic M2 and M3 receptors and adrenergic beta 3 receptors, and it is innervated by cholinergic (parasympathetic) and noradrenergic (sympathetic) fibres for contraction and relaxation, respectively.[7] The urethra has abundant adrenergic alpha 1 A/D receptors and nicotinic receptors, and it is innervated by noradrenergic (sympathetic; contraction) and cholinergic (somatic; contraction) fibres. The LUT performs two opposite functions involving the storage and emptying of urine, both of which require an intact neuraxis that involves almost all parts of the nervous system.[8] This mechanism is in contrast to postural hypotension, which arises due to lesions below the medullary circulation centre in humans.[9] *Normal urinary storage* is dependent on the spinal (sacral, bladder-inhibitory) autonomic reflex.[7,10] The storage reflex is thought to be tonically facilitated by the brain, particularly the pontine storage centre.[11,12] The pontine storage centre lies just ventrolateral to the pontine micturition centre (PMC). In addition to the pontine storage centre, the storage function is facilitated by the hypothalamus, cerebellum, basal ganglia, and frontal cortex. These areas have been shown to be activated during urinary storage using functional neuroimaging in humans.[13] *Normal micturition* is dependent on the brainstem (spino-bulbo-spinal, bladder-facilitatory) autonomic reflex and involves the midbrain periaqueductal gray matter (PAG)[14,15,16,17] and the PMC.[7,11] The PAG is thought to be central in regulating micturition and has a range of inputs from higher structures. The PMC is located in and adjacent to the locus coeruleus.[18,19,20] The PMC is thought to project spinal descending fibres containing glutamate as a facilitatory neurotransmitter to activate the sacral bladder preganglionic nucleus.[21] The PMC also projects fibres to sacral interneurons containing gamma-amino-butyric acid (GABA) and glycine as inhibitory neurotransmitters to suppresses the sacral urethral motor nucleus (the Onuf's nucleus).[22] The voiding function is initiated and facilitated by higher brain structures, for example, the hypothalamus and prefrontal cortex, which overlap in the storage-facilitating area.[13,23]

Detrusor Overactivity of Brain Origin

Bladder (detrusor) overactivity (DO) is the major cause of overactive bladder (OAB: urinary urgency/frequency) and incontinence.[24] In lesions above the brainstem, the micturition reflex arc is intact, and DO is considered to be an exaggerated micturition reflex.[24,25,26] The exaggeration of the micturition reflex may be due to more than simply the decreased inhibition of the brain, including further facilitation by glutamatergic and D2 dopaminergic mechanisms.[27]

Brain Dopamine and Micturition

The net effect of the basal ganglia on micturition is thought to be inhibitory[7,28,29,30] Functional neuroimaging during bladder filling shows the activation of the globus pallidus in normal volunteers[31] and in the putamen in patients with PD[32] (LOE2). In contrast, dopamine transporter imaging was lower in PD patients with urinary dysfunction than in those without this symptom.[33,34] Electrical stimulation of the substantia nigra pars compacta (SNc) inhibited the micturition reflex, [35,36] and striatal dopamine levels in situ significantly increased during the urinary storage phase in experimental animals.[37] The micturition reflex is under the influence of dopamine (both bladder-inhibitory by D1 and facilitatory by D2) and GABA (inhibitory).[7,28] Both SNc neuronal firing and released striatal dopamine activate the dopamine D1-GABAergic *direct pathway*, which inhibits the basal ganglia output nuclei and may inhibit the micturition reflex via GABAergic collaterals to the micturition circuit, [37,38,39,40] including the PAG.[41] In PD, disruption of this pathway may lead to DO and the resultant urinary urgency/frequency. In addition to nigrostriatal fibres, the ventral tegmental area (VTA)-mesolimbic dopaminergic fibres are thought to be involved in the control of micturition.[36,42,43]

Frontal Cortex and Micturition

The frontal cortex has been regarded as the higher centre (mainly bladder inhibition) for micturition[44] because lesions in the frontal cortex, for example, the prefrontal cortex, medial superior/middle frontal gyri, anterior cingulate cortex and supplemental motor area, produce DO in humans.[8,45,46] Functional neuroimaging in normal volunteers using positron-emission tomography (PET) and functional magnetic resonance imaging (fMRI) showed brain activation in response to bladder fullness and urination[8,47]; furthermore, the activated areas strikingly overlapped with the lesions described in clinical studies. Women with urgency incontinence show frontal deactivation when compared with control subjects.[48] The frontal cortex has direct fibre connections with the hypothalamus and the PAG, and it may regulate micturition via the basal ganglia circuit as indicated by experimental[49] and fMRI studies[50,51] (LOE2).

PATHOPHYSIOLOGY OF BLADDER DYSFUNCTION IN PD

Epidemiology and Prevalence of Bladder Dysfunction in PD

PD is the second most common neurodegenerative condition in the elderly. Although predominantly a movement disorder, PD is commonly associated with non-motor symptoms, including neuropsychiatric disturbances, sleep disorders, and autonomic symptoms.[1] LUT symptoms (LUTS), specifically nocturia, are the most common manifestation of autonomic dysfunction and are estimated to be present in up to 75% of patients[2] (LOE2). These symptoms have an immense impact on QOL measures, early institutionalisation, and health-related costs.[4]

Urodynamic Findings and Relevant PD Pathology

In health, nigrostriatal dopaminergic pathways influence the micturition reflex. Activation of the D1 receptors mediates the indirect pathway of the striatum and inhibits the reflex, whereas activation of the D2 receptors mediates the indirect pathway and facilitates this reflex. The net effect of the basal ganglia on the micturition reflex is inhibitory.[52] PD is characterised by degeneration of dopaminergic neurons in the substantia nigra, a loss of dopaminergic nigrostriatal pathways, and decreases in biochemical markers, such as dopamine, tyrosine hydroxylase, dopamine metabolites, and the dopamine transporter. The neurodegenerative changes that occur in PD can result in DO during bladder filling and has been documented in a wide range of patients, 45–93%, in urodynamics studies.[53] Functional neuroimaging during bladder filling showed activation of the globus pallidus in normal volunteers and in the putamen of PD patients with DO[54] (LOE2). In contrast, dopamine transporter imaging (indicative of brain dopamine neurons) was decreased in PD patients with urinary dysfunction when compared with patients without LUTS[33,34] (LOE2). DO correlates with the stage of PD and becomes more prevalent as the disease advances.[55] Deep brain stimulation in the subthalamic nucleus results in amelioration of motor symptoms, increases bladder capacity and decreases post-void residual urine (PVR) (LOE2). Therefore, bladder dysfunction in PD may reflect degeneration of the nigrostriatal dopaminergic cells associated with specific motor disorders. In addition to nigrostriatal dopaminergic projections, the ventral tegmental area (VTA, the A10 cell group)-limbic cortex and the hypothalamic (the A11 cell group)-spinal cord dopaminergic projections are presumably involved in urinary dysfunction in PD. Urodynamics also revealed latent detrusor weakness during voiding[56]; however, the PVR is minimal in PD.

Both storage symptoms (OAB: urinary urgency, urinary frequency, nocturia, and incontinence) and voiding symptoms (e.g., hesitancy, interrupted or poor stream, and double voiding) are reported in PD.[52] Approximately 38–71% of patients with PD report these symptoms[57,58] (LOE2). The severity of LUTS increases with the progression of PD and parallels other autonomic dysfunction.[59] LUTS are also associated with other features, such as falls.[60] In a study of PD and multiple system atrophy (MSA) patients, Sakakibara et al.[61] (LOE2) found urinary symptoms in 72% of PD patients that were mainly attributed to DO (81%) and external sphincter relaxation problems (33%). During micturition, PD patients did not demonstrate detrusor-sphincter dyssynergia; however, detrusor-hypocontractility was observed in 66% of women and 40% of men. In addition, patients with PD had mild outlet obstruction, for example, a mean Abrams-Griffiths number (outflow obstruction >40) of 40 in women and 43 in men. Nevertheless, the average volume of post-void residuals in PD was only 18 ml (LOE2). These urodynamic findings are similar to untreated, early PD patients.[62]

Nocturia is defined by the International Continence Society (ICS) as waking up at night one or more times to void,[63] and it is the most common LUTS reported in up to 70% of patients (LOE2). Nocturia has a considerable impact on QOL[6,64,65] and is associated with sleep disturbances,[66,67,68,69] falls,[70] hip fractures and greater mortality.[71,72,73] Nocturia affects the sleep of carers and partners, and it has a detrimental impact on their QOL.[74,75] One void per night may not be bothersome; however, a recent population-based study showed that two voids or more is associated with an impaired health-related QOL.[76,77] The causes for nocturia are poorly understood.[78] Currently, three possible mechanisms have been suggested: sleep disorders (insomnia), reduced bladder capacity and DO, and nocturnal polyuria[79] likely due to a slight reduction of cardiac (increased brain natriuretic peptide) or hypothalamic (decreased nighttime arginin vasopressin) function.

DRUG TREATMENT AND DEEP BRAIN STIMULATION

PD Drugs and LUTS

Bladder dysfunction is common in PD.[80,81,82] Bladder dysfunction substantially affects the QOL and correlates with neurological disability[83] and the stage of PD.[5] These latter aspects suggest a relationship between brain dopaminergic degeneration and LUTS. Urodynamic studies in PD showed DO in both treated and untreated PD patients.[39,84] This result occurs because the net effect of the basal ganglia on micturition is thought to be inhibitory.[36] The micturition reflex is under the influence of nigrostriatal dopamine and GABA inhibitory pathways. Therefore, urinary dysfunction in PD may reflect degeneration of the nigrostriatal dopaminergic cells associated with motor disorders.

The main families of drugs useful for treating motor symptoms are levodopa, dopamine agonists, and monoamine oxidase type B (MAO-B) inhibitors.[85] As shown below, drugs to treat motor dysfunction can significantly affect (either ameliorate or worsen) bladder function in PD.

Levodopa. L-Dopa is a precursor of dopamine and has been the standard therapy for motor dysfunction in PD patients for more than 30 years. Levodopa is readily converted into dopamine by dopa-decarboxylase. To reduce the peripheral metabolism of levodopa, it is combined with a peripheral dopa-decarboxylase inhibitor (i.e., carbidopa or benserazide). The dose of levodopa should be kept as low as possible to maintain good functioning and to reduce the development of drug-induced complications (e.g., wearing-off, on-off, dyskinesia, and hallucinations).[85,86]

To date, the effect of levodopa on LUTS in PD patients remains unclear. Previous animal and human studies demonstrated that acute D2 receptor activation worsens bladder function.[6,28,30,87] In contrast, studies in normal rats[28] and parkinsonian monkeys[30] demonstrated that the tonic activation of D1 receptors inhibits bladder voiding. A logistic regression analysis of 3,414 PD patients found that urinary (OAB with/without urinary incontinence) and other non-motor symptoms were often not responsive to levodopa therapy[88] (LOE2).

There are several factors underlying the complex bladder behaviour in PD patients. Post-synaptic dopamine D1 (excitatory) and D2 (inhibitory) receptors have different affinities to dopamine. Dopamine's affinity for D1 receptors ($Ki = 5$ to $10\,\mu M$) is lower when compared with D2 receptors ($Ki = 0.5\,\mu M$).[89] Furthermore, dendritic D2 (inhibitory) autoreceptors have the highest (picomolar) affinity for dopamine. Based on

these biochemical parameters, it is likely that the D2-mediated effect prevails over the D1-mediated effect after acute levodopa administration in naive patients, which might suppress the nigral cells and facilitate the micturition reflex. As observed in chronic levodopa therapy PD patients, an acute levodopa challenge produces a higher synaptic concentration of the drug optimal for D1 and D2 activation which can inhibit bladder voiding and improve bladder function[36,52,90] (LOE2). A long-term levodopa treatment can cause a down-regulation of dopamine receptors that correlates with the development of motor fluctuations.[52,91] Currently, randomized clinical trials (RCTs) and meta-analyses are not available.

Dopamine agonists. To avoid drug-induced motor complications, the strategy to delay the start of levodopa has been developed by introducing dopamine agonists. Dopamine receptor agonists mimic the effect of dopamine by binding directly with the post-synaptic dopamine receptors. This class of drugs can be classified as ergolinine (bromocriptine, pergolide, cabergoline, lisuride) or non-ergolinine (pramipexole, ropinirole, apomorphine) drugs.[85]

Some reports have shown storage-facilitating effects of dopaminergic drugs. A questionnaire study reported that voiding symptoms (intermittency and sensation of residual urine) were more common in patients taking levodopa and bromocriptine (D2-selective agonist) than in those taking levodopa alone.[8] In contrast, Kuno et al. showed that a change from bromocriptine to pergolide (D1 < 2 agonist) lessened nocturia[92] (LOE3). Apomorphine is a widely used third-line treatment for PD. Apomorphine was reported to increase bladder capacity[93] (LOE3). Currently, neither RCTs nor meta-analyses are reported in the literature.

MAO-B inhibitors (monoamine oxidase type B inhibitors). MAO-B inhibitors block the metabolism of dopamine, thereby increasing its level in the striatum.[85] Two compounds of the propargylamine group, selegiline and rasagiline, are irreversible MAO-B inhibitors that have demonstrated a symptomatic effect in PD patients; however, no specific urinary effect was described until recently.[78] Rasagiline, a new generation MAO inhibitor, is under investigation for its role in bladder disturbances in early mild PD patients. Rasagiline may increase dopamine post-synaptic concentrations at the central level. In a very recent preliminary report,[94] rasagiline was found to improve the urodynamics and clinical findings of early mild PD patients (LOE2).

LUTS Drugs and PD

Bladder dysfunction frequently occurs in PD patients,[80,81,82] and OAB symptoms are the most common.[95] OAB can occur in early and untreated PD patients[36,95] (LOE2). Currently, anticholinergics are the main treatment for OAB in PD, which is similar to the treatment regimen of OAB in the general elderly population. Pharmacological therapy is particularly helpful in early, mild neurogenic bladder dysfunction. Patients with more profound bladder dysfunction may require other forms of management that are discussed later in this review.

The most common classes of agents are antimuscarinics and alpha-adrenergic antagonists. However, most drugs have not been specifically evaluated in neurogenic bladder dysfunction, including PD.

Drugs for Storage LUTS

Antimuscarinics. Antimuscarinic therapy is the main treatment for OAB and neurogenic DO. Anticholinergics are considered to be both safe and effective, including for the long-term treatment of neurogenic DO.[96] However, there have been no double-blind, placebo-controlled, randomised studies specifically for PD patients taking antimuscarinics. Centrally-acting anticholinergic drugs (e.g., trihexyphenidil) are widely used to treat parkinsonism; however, these drugs can increase the risk for cognitive-related adverse events.[97] Antimuscarinics may increase post-void residual (PVR) urine; therefore, regular PVR measurements using ultrasound are needed.

Oxybutynin. Oxybutynin is a non-selective, competitive antagonist of the M1, M2, and M3 subtypes of the muscarinic acetylcholine receptor. It is a moderately potent antimuscarinic agent with a pronounced muscle relaxant activity.

Oxybutynin is the most studied antimuscarinic in the treatment of bladder dysfunction in PD patients. In 2003, a Cochrane systematic review of anticholinergic use (centrally acting) to treat PD was completed by Katzenschlager et al. This single study involved two anticholinergic drugs[98] (LOE2). Cognitive adverse events of oxybutynin are a concern, particularly in elderly PD patients. This concern was first described by Donellan et al. who reported four cases of acute confusional states in elderly patients with a pre-existing cognitive impairment treated with oxybutynin[99] (LOE2). This cognitive dysfunction reversed after discontinuation of oxybutynin. The effect was mainly due to a high M1-receptor selectivity and the easy penetration of the blood brain barrier (BBB)[100] (LOE2).

Bennett et al.[101] evaluated the efficacy and tolerability of higher doses of oxybutynin chloride in patients with a neurogenic bladder and multiple sclerosis, spinal cord injury or PD. Only seven PD patients were enrolled in the study. A 7-day washout period was used before initiation of the starting dose of 10 mg OXY-XL. Doses of OXY-XL were increased by 5 mg at weekly intervals to a maximum dose of 30 mg per day guided by patient perception of efficacy versus side effects. At the end of the study, statistically significant decreases in the number of voids over 24 hr, episodes of nocturia and incontinence episodes were observed. Residual urine remained unchanged. No patient experienced serious adverse events.[101] Currently, no other specific well-designed PD studies have reported on the clinical use of oxybutynin.

Propiverine. Propiverine is an antimuscarinic agent with a mixed mode of action that is used for the treatment of symptoms associated with OAB. As well as blocking muscarinic receptors in the detrusor muscle, this drug also inhibits cellular calcium influx, thereby diminishing muscle spasms.[102]

A MEDLINE search did not reveal any specific PD-based studies. However, a review of neurogenic DO showed that propiverine and oxybutynin were equally effective at increasing bladder capacity and lowering bladder pressure with a trend of an amelioration of dry mouth.[103] Propiverine does not easily penetrate the BBB. Therefore, propiverine can be added-on as a peripherally-acting OAB drug in combination with centrally-acting dementia drugs[104] (LOE2).

Trospium. Trospium is a quaternary ammonium derivative with mainly antimuscarinic actions. Being a quaternary amine, trospium has a high polarity that may limit blood-brain barrier penetration and cognitive adverse events. The currently available literature does not include studies focused on the use of trospium in PD; however, this molecule significantly reduced the number of urinations, increased cystometric capacity and the mean effective volume of the bladder, and reduced the incidence of urgent voids in neurogenic patients. Staskin et al. showed that trospium does not cross the BBB of healthy elderly individuals[105] (LOE2). The EAU guidelines recommend that trospium is given

to cognitively impaired patients when compared with anticholinergics.

Tolterodine. Tolterodine acts mainly on M2 and M3 muscarinic receptors. Currently, no specific well-designed PD studies have reported on the clinical use of tolterodine.

In people with neurogenic DO, tolterodine was comparable with oxybutynin at enhancing bladder volume and improving continence. Dry mouth was less common. Jost suggests that tolterodine does not cross the BBB, thus reducing cognitive adverse events.[106]

Solifenacin. Solifenacin is a competitive cholinergic receptor antagonist. The binding of acetylcholine to these receptors, particularly the M3 receptor subtype, plays a critical role in the contraction of smooth muscle. Although extensively studied in OAB and recommended for use in PD patients,[106,107] solifenacin has not been specifically studied for its effect on LUTS in PD clinical cases.

Darifenacin. Darifenacin works by blocking the M3 muscarinic acetylcholine receptor. This antimuscarinic drug has been extensively studied in OAB but not in neurogenic bladder dysfunction. Being a highly selective M3 receptor anticholinergic, darifenacin may be used for avoiding cognitive disorders[106,107] (LOE2).

Fesoterodine. Fesoterodine is a prodrug. It is broken down into its active metabolite, 5-hydroxymethyl tolterodine, by plasma esterases. There is no current data on the effect of fesoterodine in neurogenic LUT dysfunction and PD.

Mirabegron. Mirabegron activates the β3 adrenergic receptor in the detrusor muscle of the bladder, which leads to muscle relaxation and an increase in bladder capacity. Currently, no specific well-designed PD studies have assessed the clinical use of mirabegron.

Botulinum neurotoxin type a (BoNT/A). Following several publications from an increasing numbers of centres worldwide and other multicentre registration studies, the intravesical injection of BoNT type A (BoNT/A) using onabotulinumtoxinA (BOTOX™) has become the newest approved treatment for urinary incontinence in adult neurological patients with an inadequate response to (or reduced tolerance of) anticholinergic medications (U.S. Food and Drug Administration approval). Similar approval has been granted or is awaiting in a number of European countries.[108]

Almost all studies have published on two BoNT/A preparations, including onabotulinumtoxinA (Botox) and abobotulinumtoxinA (Dysport). These two formats are not interchangeable, and there are no direct comparisons for dose, efficacy and safety for urological indications. Although both products appear to be efficacious in NDO, onabotulinumtoxinA has been more comprehensively studied than abobotulinumtoxinA.[109]

In 2009, Giannantoni et al. analysed four patients with PD and 2 patients with multiple system atrophy (MSA). All patients received 200 U of botulinum toxin type A injected into the detrusor muscle at 20 sites under cystoscopic guidance during a single inpatient session. The authors showed that botulinum toxin type A injections into the detrusor muscle was an effective and safe treatment for refractory OAB symptoms and DO related to PD[110] (LOE2). Two years later, the same group used half of the drug dose to repeat the study. Eight patients with PD and DO refractory to anticholinergics were injected with 100 U of botulinum toxin type A. This intradetrusor injection of 100 U botulinum toxin type A induced clinical and urodynamic improvement in OAB symptoms that lasted for at least 6 months in patients with PD[111] (LOE2).

In 2010, Kulaksizoglu et al. demonstrated that an intravesical botulinum toxin injection is an effective treatment modality with local action and no central nervous system side effects in patients with PD. The intradetrusor injection technique with a 30-point template was employed. Sixteen patients received 500 i.u. of botulinum toxin-A[112] (LOE2).

In 2014, Anderson et al. presented their study on twenty patients with PD and incontinence to evaluate the safety and effectiveness of low-dose (100 U) onabotulinumtoxinA (onabotA) bladder injections as an office procedure with topical anaesthesia. The authors concluded that office cystoscopy with a low-dose onabotA injection treatment is a potential long-term management strategy for patients with PD and urinary incontinence who do not respond to oral antimuscarinic agents[113] (LOE2).

Drugs for Voiding LUTS

Alpha blockers. Alpha-adrenoceptors are present in the bladder base, posterior urethra and prostate. Alpha-blockers have been reported to be useful for the treatment of neurogenic bladder by decreasing urethral resistance during voiding.[109]

Selective α1-adrenergic blockers include alfuzosin, prazosin, doxazosin, tamsulosin, terazosin, silodosin. A MEDLINE search did not reveal a specific alpha-blocker-PD tailored study. Alpha-blockers may worsen the postural hypotension that may occur in PD.

Botulinum toxin. Historically, sphincter injections were the first application of BoNT/A in the LUT[114]; however, there is still inadequate evidence to support its use. Some papers highlighted the role of botulinum toxin as an emergent treatment for autonomic dysfunction in PD.[107,115]

As mentioned above, Anderson et al. analysed the effect of low-dose (100 U) onabotulinumtoxinA (onabotA) bladder injections. Twelve of twenty patients were males, and the authors concluded that the treatment can be safely utilised in older men with BPH and concomitant PD and incontinence [113] (LOE2).

Deep brain stimulation for LUTS. Deep brain stimulation (DBS) of the subthalamic nucleus (STN) has been established as a surgical treatment for motor symptoms in PD patients.[116] However, data from experimental urodynamic measures in animal models[39,117] and in men[118,119] demonstrated a significant influence of STN-DBS on urinary bladder function. In humans, Seif et al. demonstrated that the main effect of STN-DBS was a normalisation of urodynamic parameters in the storage phase with a delayed first desire to void and an increased bladder capacity[119] (LOE2).

In 2008, Herzog et al.[120] published a study that investigated how STN-DBS modulates the processing of urinary bladder information to elucidate the pathophysiology of sensory gating mechanisms in PD. Nine PD patients with bilateral STN-DBS switched on (STN-DBS ON) or off (STN-DBS OFF) were studied under dynamic bladder filling and empty bladder conditions (for control) for changes in regional cerebral blood flow using PET. Urinary bladder filling led to an increased rCBF in the periaqueductal grey (PAG), the posterior thalamus, the insular cortex, the right frontal cortex and the cerebellum bilaterally. A significant interaction between bladder conditions and STN-DBS was observed in the posterior thalamus and the insular cortex, including an enhanced modulation of these areas during STN-DBS ON when compared with STN-DBS OFF. Furthermore, regression analyses revealed a modulation of the neural activity in the thalamus and the insular cortex by AG activity during STN-DBS ON only. Thus, STN-DBS led to a significant

enhancement of afferent urinary bladder information processing. These data suggest that STN-DBS facilitates the discrimination of different bodily states by supporting sensory perception and underlying neural mechanisms. Furthermore, this is the first imaging study to show an effect of STN-DBS on sensory gating in PD patients and its neural basis[120] (LOE2).

In 2012, Winge et al.[121] enrolled and compared 107 patients with advanced PD receiving oral medications with patients treated using either DBS in the subthalamic nucleus or with an apomorphine pump. The study revealed that patients treated with DBS in the STN had a similar amount of LUTS as patients treated with either conventional oral medication therapy or an apomorphine pump; however, these patients exhibited significantly less nocturia ($P = 0.007$)[121] (LOE2).

Although DBS may be a promising therapy for LUTS based on a small number of studies, a very low number of cases described a worsening of urological disorders.

In 2008, Kessler et al.[122] investigated seven patients (two females, five males) with essential tremor 15-85 months after implantation of DBS leads into the ventral intermediate (Vim) nucleus of the thalamus. The authors compared urodynamic parameters during thalamic DBS (ON state) and 30 min after turning off the stimulator (OFF state). There was a significant decrease in bladder volume at first desire to void, at strong desire to void, and at maximum cystometric capacity in the ON state when compared with the OFF state. No significant differences between the ON and OFF state were detected for changes in detrusor pressure during filling cystometry, bladder compliance, maximum detrusor pressure, detrusor pressure at maximum flow rate, maximum flow rate, voided volume, and post-void residual urine. The authors concluded that thalamic DBS resulted in an earlier desire to void and decreased bladder capacity, suggesting a regulatory role of the thalamus in LUT function. Therefore, the thalamus may be a promising target for the development of new therapies for LUT dysfunction[122] (LOE2).

In 2011, Aviles Olmos et al.[123] studied low-frequency DBS of the pedunculopontine nucleus (PPN), which has been reported to improve akinesia and gait difficulties in patients with PD. The authors reported the case of a patient with PD and L-dopa refractory gait symptoms who developed DO immediately after a right PPN DBS. They suggested that the proximity between the caudal PPN and brainstem structures implicated in control of micturition was a possible explanation for DO development[123] (LOE2).

Other Treatments

Bladder dysfunction is a common non-motor symptom in PD.[123,124] Among LUTS, nocturia (night-time urinary frequency) is the most prevalent symptom (>60%).[5,18,49,125] Pharmacologic approaches to bladder dysfunction are limited because bladder dysfunction, in contrast to motor symptoms, is often nonresponsive to levodopa treatment.[123] Anticholinergic drugs offer the most practical alternative to DO; however, limitations are frequent, including non-responders, constipation and cognitive impairment in elders. LUTS were more common in a group older-aged PD patients and healthy populations. In a prospective review of 110 PD patients, the severity of the neurological disease was the only predictive factor for the occurrence of voiding dysfunction, which affected both men and women. Sixty-three (57.2%) patients were symptomatic.[126] Other studies did not report an increase in the frequency and severity of LUTS as PD progressed; however, patients found the symptoms more bothersome. This outcome may be due to a progression in gait difficulties and/or a decreasing ability to separate and integrate sensory input.[127]

Concomitance with an increased prevalence of other causes of urinary symptoms, such as benign prostate hyperplasia (BPH) in males and stress urinary incontinence (SUI) in females, makes treatment more challenging and an individualised decision. Here, we discuss how to manage concurrent BPH in PD patients; however, bladder management in neurologic patients lacks evidence from a large scale study, including PD patients.[128,129]

PD and BPH Surgery Should Exclude MSA, a More Progressive Disorder

Both PD and BPH are common in late middle-aged men; thus, their coincidence is probable. The symptoms of BPH include voiding difficulty, frequency, urgency and night-time frequency. These symptoms are also common and troublesome in the later stages of PD.[131,132] PD starts insidiously; therefore, there may be considerable diagnostic difficulties in its early stage, particularly in men with mild PD and LUTS[131] (LOE3). In typical BPH patients, urodynamic studies with pressure flow analyses demonstrated high-pressure low-flow obstructive patterns with or without DO (particularly terminal DO) (LOE2).

A urodynamic study of men sought to identify differences between DO due to BPH (non-neurogenic DO) and DO due to PD (neurogenic PD).[139] Three groups of patients were studied: group one included men with LUTS and no known neurologic condition with DO (n = 22), group 2 included men with PD and LUTS (n = 39), and group 3 included women with PD and LUTS (n = 18). Men with non-neurogenic LUTS were less likely to have urgency incontinence or UDS than either men or women with PD. DO due to PD occurred earlier during filling when compared with non-neurogenic DO, especially in women.[139] Patients with BPH should be warned that symptoms of an OAB might not resolve following prostatectomy because they may be due in part to an underlying neurological disorder (such as PD) or its treatment[130] (LOE2).

Nevertheless, to maximise patients' QOL, men with a definitive diagnosis of PD and coincidental BPH should be considered for appropriate surgery. PD is no longer be considered a contraindication for transurethral resection of the prostate (TURP), and preoperative investigations, including urodynamic assessment, should be used to confirm the diagnosis of PD and BPH[140] (LOE2). A retrospective study of 23 men with PD and benign prostatic outflow obstruction who underwent TURP was completed.[140] Patients with MSA were excluded from this analysis. The median patient age was 73 years, the median duration of PD before TURP was 3 years, and the median Hoehn and Yahr scale was 2. Out of the 14 patients with a preoperative indwelling urinary catheter, TURP restored voiding in 9 patients (64%), and only 5 patients (36%) required catheterisation postoperatively. Thus, TURP for BPH in patients with PD may be successful in up to 70% of patients, and the risk of de novo urinary incontinence is minimal.

The use of alpha blockers in mild/moderate obstructions offers limited but positive voiding improvement with poor results in patients with more severe neurological impairments.[141] Patients who are able to contract the sphincter are unlikely to develop urgency urinary incontinence after a prostatectomy, whereas the risk of post-prostatectomy incontinence is high in those who are unable to voluntarily contract the sphincter ani[136,142] (LOE3). Thus, a sphincter electromyography (EMG) evaluation should be performed prior to the prostatectomy.[136,138] The incidence of incontinence in men undergoing radical prostatectomy for prostate cancer appears to be similar for patients with and without PD; however, there is no strong evidence for this conclusion.

Multiple system atrophy (MSA) is a disease that simulates PD but is more progressive and leads to urinary retention (formerly called Shy-Drager syndrome). There is a consensus between experts that the incontinence of MSA rarely improves after prostate surgery. If there is a clinical suspicion that a patient has MSA, only non-surgical management of bladder symptoms should be considered[130] (LOE2). Therefore, proper diagnosis of MSA before performing prostatic surgery is extremely important. Approximately 50% of patients with MSA are initially misdiagnosed as having PD[130] (LOE2). The incidence of MSA versus PD is approximately 1:10. MSA can present either as a poorly levodopa-responsive parkinsonism (MSA-P) or a cerebellar dysfunction (MSA-C); however, in either condition, additional bladder dysfunction causing urinary incontinence is an early feature.[131] The differential diagnosis between MSA-P and PD can be difficult even for neurologists who specialise in movement disorders. However, early troublesome incontinence and even earlier erectile dysfunction in men are now regarded as warning signs of MSA.[131]

Urodynamic investigations in patients with MSA commonly show DO as the underlying cause of OAB symptoms, which is indistinguishable from that in PD.[132] In contrast, a useful discriminator for the differential diagnosis of MSA from PD includes incomplete bladder emptying (post-void residuals [PVR] >100 ml).[123,134] Incomplete bladder emptying worsens with progression of MSA.[132] A study measuring the PVR volume in MSA patients found an increase in mean PVR between the first and fifth years.[133] This phenomenon is in clear contrast to PD, where patients commonly report hesitancy and a poor urinary stream; however, the PVR is typically low.[123] Another predictor of MSA was an open bladder neck at the start of bladder filling without accompanying DO, which was found in 53% of patients with MSA but no PD patients[132] (LOE2). This finding indicates internal sphincter denervation.[132] The most important predictor of MSA was the neurogenic change of sphincter EMG, which is rarely seen in patients with PD. This simple test can differentiate MSA from PD[130,131,132] (LOE2). Urodynamics and neurologic evaluations are imperative in suspected PD patients if the response to anticholinergics is unsatisfactory, incontinence is a problem, or when an indwelling catheter is needed[137] (LOE2).

Intravesical Botulinum Toxin Injection to Treat Intractable DO in PD

Intravesical botulinum toxin injection is considered to be a promising method to treat intractable DO in PD. Only two studies have specifically reported on this topic. Giannantoni et al. investigated the effectiveness and safety of botulinum toxin type A injected into the detrusor muscle in patients with PD and MSA who had refractory OAB symptoms and DO[143] (LOE3). Four patients with PD and 2 patients with MSA were enrolled in the study. To avoid the urinary dysfunction due to prostatic hypertrophy commonly present in male patients, female patients were analysed. All patients received 200 U of botulinum toxin type A (onabotulinuntoxim A—"Botox") injected into the detrusor muscle at 20 sites under cystoscopic guidance during a single inpatient session. Three months after the injection, all patients reported a decrease of daytime and night-time urinary frequency and improved QOL scores. However, in all patients the PVR volume increased and intermittent catheterisation (CIC) was required in patients with MSA. A cut-off value of 150 ml for the PVR volume was used for the start of intermittent bladder catheterisation.

Another study included 10 female and 6 male PD patients who were followed for 12 months. The mean age of the patients was 67.2 years. The average duration of the illness was 6 years and the median Hoehn and Yahr stage was three[144] (LOE3). All patients received 500 i.u. of botulinum toxin-A (abobotulinuntoxim A—"Dysport") diluted to a total of 30 cc with isotonic saline. Injections were performed in 1 mL portions above the inter-ureteric ridge covering both lateral walls, the base and the back wall of the bladder but not into the dome. Overall voiding frequency improved in all patients. However, six patients were almost completely incontinent and used diapers, and thus the daily urinary frequency would be skewed. PVR urine is a major concern after botulinum toxin-A injections; however, none of the patients needed intermittent or indwelling catheterisation after the procedure. There appeared to be no change in the neurological status of the patients post-injection.

There are some concerns regarding the data in the aforementioned studies. A total of twenty PD patients were injected but only four were men. The types of botulinum toxin A used were different (onabotulinuntoxim A and abobotulinuntoxim A); therefore, the data are not fully comparable regarding action and dose effects. As reported by Giannantoni, two MSA patients needed intermittent catheterisation because MSA is a more progressive disorder that leads to urinary retention. Therefore, it is important to differentiate MSA from PD before completing botulinum injections. Currently, no recommendation for dosages, risk factors for retention or difficulty voiding or long-term effectiveness are available.

Posterior Tibial Nerve Stimulation for NDO in PD

Kabay et al. evaluated the acute effects of posterior tibial nerve stimulation (PTNS) on the urodynamic findings in PD patients with DO (described by the authors as neurogenic DO)[145,146] (LOE2). Thirty-two patients (19 men and 13 women) were included in the study. Electrical stimulation was applied unilaterally from the medial malleolus and posterior to the edge of the tibia using charge-compensated 200 msec pulses with a pulse rate of 20 Hz. The authors demonstrated that PTNS had an acute effect of suppressing DO in PD patients. Bladder capacity with PTNS was improved. The authors concluded that these findings are encouraging for further evaluation of the effective use of PTNS in clinical practice for DO in PD patients. These data should be verified with a prospective multicentre study before it is introduced in routine clinical practice.

CONCLUSIONS

LUT dysfunction is common in PD. Disruption of the dopamine D1-GABAergic direct pathway may lead to LUTS in PD, and OAB is the most common LUTS in these patients. Objective assessment using urodynamics often shows DO and a minimal PVR; however, subclinical detrusor weakness during voiding may occur. With regards to bladder management, it is well recognised that dopaminergic drugs can improve or worsen LUTS in PD. Therefore, an add-on therapy with anticholinergics is required. A beta-3 adrenergic agonist can be used as a treatment option because of its little to no central cognitive effects. Newer interventions, such as DBS, is expected to improve bladder dysfunction in PD. Botulinum toxin can be used for intractable urinary incontinence in PD. TURP for comorbid BPH in PD is no longer recognised as contraindicated if MSA is excluded. The collaboration of urologists with neurologists is highly recommended to maximise patients' bladder QOL.

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APPENDIX 1

A flow chart for bladder management of Parkinson's disease patients with an overactive bladder (previously diagnosed cases).

Parkinson's disease (PD) patients commonly have an overactive bladder (OAB). We use the following flow chart when seeing this type of patient (already diagnosed cases):

First, even though most bladder disorders in PD patients may be caused by PD itself, we check for common bladder diseases (Fig. A1). Among these, male PD patients over 50 years of age are checked for benign prostatic enlargement by cystoscopy and ultrasound sonography. Outlet obstruction can be determined with pressure-flow urodynamics. Similarly, female PD patients over 50 years of age are checked for stress-induced urinary incontinence (UI), e.?g., UI during physical stress, through a detailed analysis of patient history. Further detection of pelvic floor decent can be made using chain urethrocystography or stress urodynamics. PD patients over 50 years of age are checked for polyuria. A bladder diary can reveal polyuria (urine output >300 ml a day) or nocturnal polyuria (urine output night-time >33% of a day). Neurologists may start the patient on antiparkinsonian drugs for motor symptoms.

Second, the effect of antiparkinsonian drugs on OAB (drugs might be given by neurologists for motor function) is assessed.

If the OAB is ameliorated, then the antiparkinsonian drugs benefited the bladder. However, the drug may not significantly change bladder conditions.

Third, if necessary the patient is started on anticholinergic drugs for lessening OAB.

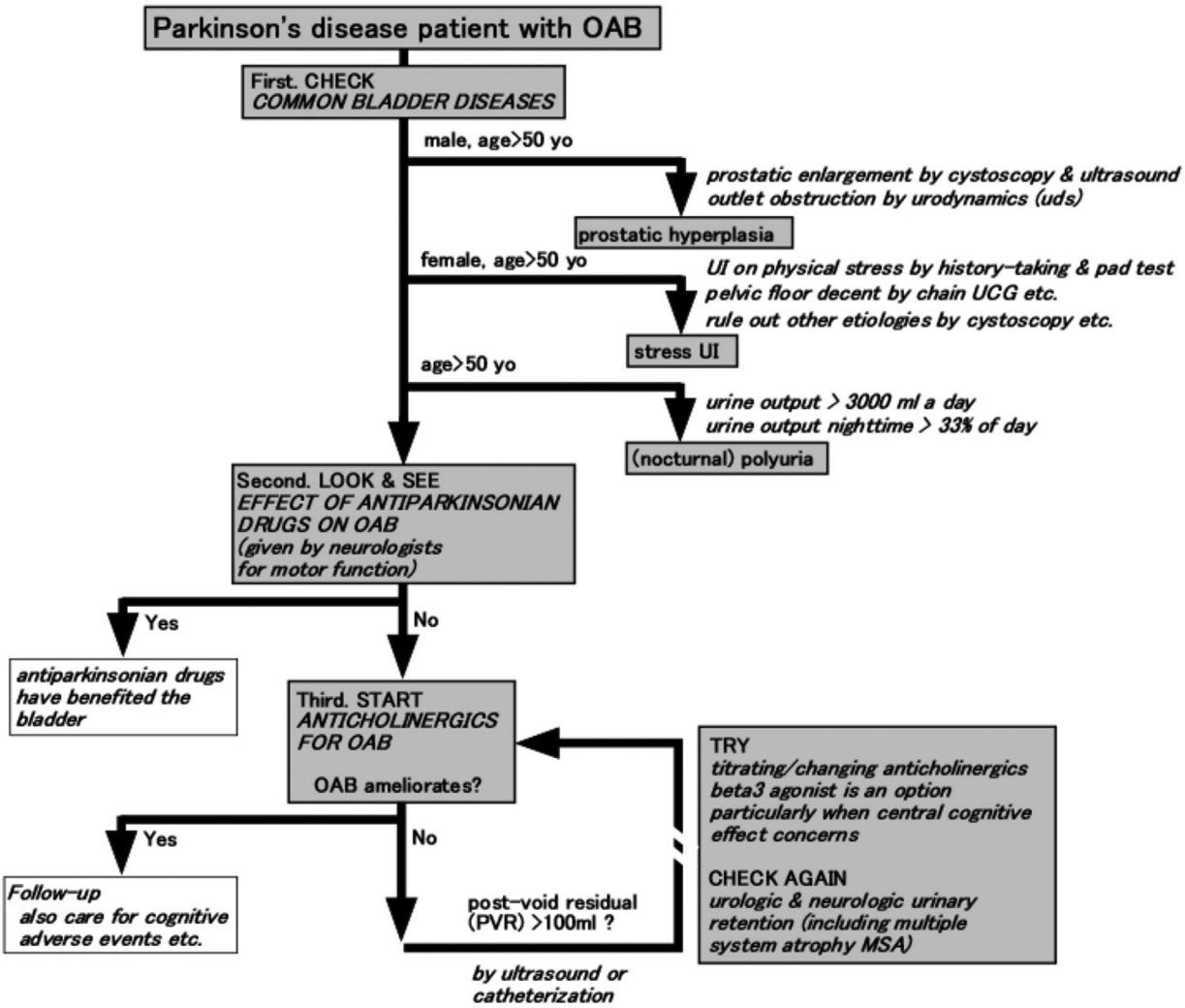

Fig. A1. A flow chart for bladder management of Parkinson's disease patients with an overactive bladder (previously diagnosed cases).

If the OAB is ameliorated, then we follow up with the bladder. We also care for cognitive adverse events by asking caregivers and patients, or performing a cognitive screening test because anticholinergics may worsen cognitive function, particularly in elderly patients. Notably, post-void residuals (PVR, by ultrasound sonography or catheterisation) may increase (more than 100 ml) if the OAB treatment does not produce significant effects.[131,147] If the PVR increases, the anticholinergic medication can be titrated or changed. In this case, we try to ascertain the urologic and neurologic causes of urinary retention, which can include multiple system atrophy (MSA).

APPENDIX 2

A flow chart of differential diagnoses of Parkinson's disease, multiple system atrophy, and other parkinsonian disorders with lower urinary tract symptoms (undiagnosed cases): a urological point of view.

Clearly, it is not the responsibility of urologists to make a differential diagnosis for neurological diseases. However, urologists should have a brief bedside strategy for the differential diagnosis of such patients because it is not uncommon that patients visit urologists first.

Elderly gait disorder/easy fall is often accompanied by LUTS. The exact reason for this is not clear. However, it is possible that both bladder and gait disorders originate presumably from the same brain lesions involving the prefrontal/mediofrontal area and basal ganglia neural circuit.[54,148,149] Gait disorders in elderly individuals are mainly parkinsonian, e.?g., slow, short-stepped gait without laterality.[150] Bladder disorders in elderly individuals consist mainly of OAB.[151]

Figure A2 illustrates how we can manage elderly individuals with gait & bladder problems.

First, common bladder diseases should be excluded. Male individuals over 50 years of age should be checked for benign prostatic enlargement using cystoscopy and ultrasound sonography. Outlet obstruction can be detected using pressure-flow urodynamics.

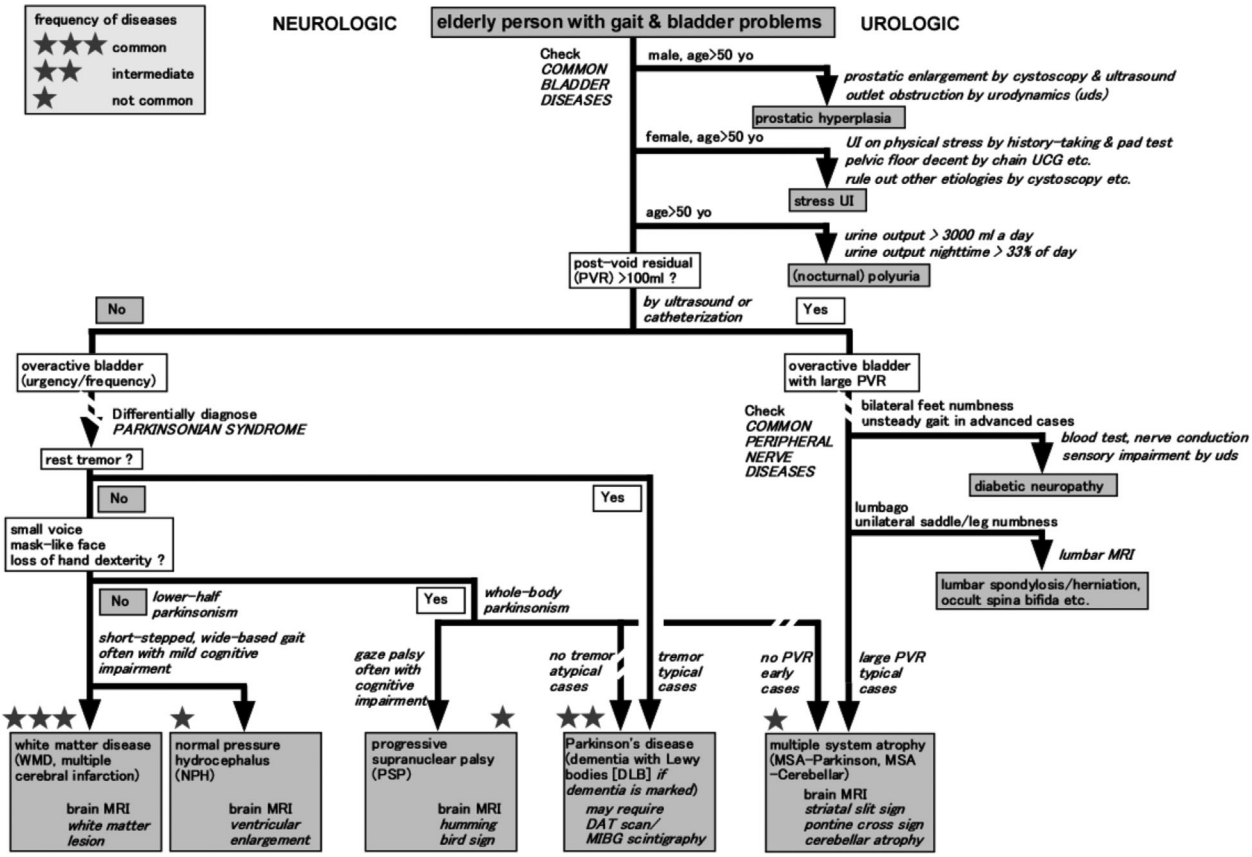

Fig. A2. A flow chart of differential diagnoses for PD, MSA, and other parkinsonian disorders with LUTS (undiagnosed cases).

Similarly, female individuals older than 50 years of age should be checked for stress urinary incontinence (UI), e.?g., UI during physical stress, through a detailed review of the patient's history. Detection of pelvic floor decent can be completed using chain urethrocystography and stress urodynamics. Individuals over 50 years of age should be checked for polyuria. A bladder diary can reveal polyuria (urine output >300 ml a day) or nocturnal polyuria (urine output night-time >33% of a day).

Second, it should be determined if the post-void residual (PVR) urine volume is greater than 100 ml using ultrasound or catheterisation.[6] If yes, common peripheral nerve diseases should be excluded because they often cause a large PVR. Diabetic neuropathy is the most likely cause for bilateral feet numbness (may have unsteady gait in advanced cases) in an elderly patient. To confirm this diagnosis, a blood test, nerve conduction study, and detection of bladder sensory impairment using urodynamics are recommended. Lumbar spondylosis (lumbar herniation, occult spina bifida in young adult) is the most likely cause of lumbago with unilateral saddle/leg numbness in an elderly patient. To confirm this diagnosis, a lumbar magnetic resonance imaging (MRI) scan is recommended. It is rare that spinal cord diseases, including multiple sclerosis, present with a large PVR alone without sensory/gait difficulties.[147,152]

If common peripheral nerve diseases are excluded, multiple system atrophy of parkinsonian type (MSA-P) is a possible diagnosis.[153,154] To confirm this diagnosis, postural hypotension and nocturnal stridor/snoring/sleep apnoea using both history-taking and tests should be completed; in addition, a brain MRI to detect striatal slit sign/volume loss, pontine cross sign, and cerebellar atrophy is necessary. Gait disorder in MSA-P can be indistinguishable from that of PD; however, disproportionate antecollis, foot dystonia, and pyramidal signs are symptoms that suggest MSA-P. The frequency of MSA-P is one star (three stars, common; two stars, intermediate; one star, not common).

If a large PVR >100 ml is absent, the elderly patient is likely to suffer from an overactive bladder (OAB) (urinary urgency/frequency). Thus, parkinsonian syndrome should be differentially diagnosed.

First, the patient should be observed for a resting tremor. If present, the patient likely has PD. When coexisting dementia is marked, the patient likely has dementia with Lewy bodies (DLB). PD subjects often have a long history of constipation and sleep-talking (also called 'REM sleep behaviour disorder' [RBD]). Some subjects report a loss of smell. To confirm this diagnosis, a brain dopamine transporter (DAT) scan to confirm dopaminergic depletion and metaiodobenzylguanidine (MIBG) myocardial scintigraphy to confirm noradrenergic depletion are necessary. The frequency of PD is two stars.

If a resting tremor is absent, the patient should be observed for small voice, mask-like face and loss of hand dexterity. If present, the subject may have parkinsonism of degenerative origin, which includes MSA-P. MSA-P may include OAB alone within 2 years after disease onset. Two years after disease onset, MSA-P often presents with a large PVR >100 ml and leads to urinary retention. Another degenerative parkinsonism is progressive supranuclear palsy (PSP).[155,156] PSP can include gaze palsy, e.?g., PSP patients cannot easily look at the direction where others come or call from. Additionally, PSP patients often have cognitive impairment. To

confirm this diagnosis, a brain MRI scan to detect the humming bird sign (emperor penguin sign) is necessary. The frequency of PSP is one star.

If small voice, mask-like face and loss of hand dexterity are absent, the subject may have parkinsonism of non-degenerative origin (lower half parkinsonism). The subject most likely has a short-stepped, wide-based gait (co-existing ataxia of frontal lobe origin) and mild cognitive impairment (also of frontal lobe origin). The most common disease with these symptoms is white matter disease (WMD) (multiple cerebral infarction).[151] WMD has three clinical features, including vascular parkinsonism (described above), vascular incontinence (OAB often precedes urinary incontinence) and vascular dementia (much milder than Alzheimer's disease). However, in most advanced cases, emotional incontinence (easy cry, etc.), frontal release signs (palmomental, snout and grasping reflexes), dysphagia and aspiration pneumonia are not rare. To confirm this diagnosis, a brain MRI scan to check for WMD is necessary. The frequency of WMD is three stars. It is important to check for normal pressure hydrocephalus (NPH) because NPH cannot be differentiated from WMD by 3 clinical signs alone (gait disorder, OAB/incontinence and dementia); furthermore, NPH is a potentially a treatable disease, e.?g., ventriculoperitonral shunt surgery.[157,158] To confirm this diagnosis, a brain MRI scan to detect ventricular enlargement with tight convexity is necessary. Recent prospective imaging studies showed that the frequency of NPH versus WMD is approximately 1:10. The frequency of NPH is one star.

Medications for OAB in patients with gait disorders other than PD have also used as a general OAB treatment regimen. The urodynamics of these patients often show detrusor overactivity (DO) during bladder filling. However, it should be mentioned that most of these patients are elderly, and their blood brain barrier (BBB) might be disrupted. [159] The use of medications with anticholinergic side effects in the elderly is concerning. By crossing the BBB, these medications can act at the M1-muscarinic receptors in the cerebral cortex and hippocampus or the M4-receptors in the basal ganglia. Factors predisposing patients to cognitive side effects include central muscarinic receptor affinity, e.?g., high M1-receptor selectivity, and permeability across the BBB, e.?g., size, lipid solubility, fewer hydrogen bonds, neutral or low degree of ionisation, and a small number of rotatable bonds.[100,160] Darifenacin is an M3-selective antagonist and has less pronounced cognitive side effects; however, trospium, a quaternary amine, has high polarity and therefore poor permeability across the BBB.[160] It was recently shown that the addition of propiverine to donepezil ameliorated OAB without worsening cognitive function in elderly OAB patients with dementia.[104] Mirabeglon, a novel adrenergic beta-3 receptor agonist, is a promising treatment for lessening DO with fewer central side effects.[161]

One exception is MSA-P because patients with MSA often need clean, intermittent catheterisation (CIC) because of an OAB and large PVR.[154,162] Patients' urodynamics often show DHIC (detrusor hyperactivity during bladder filling with impaired contraction during voiding). Therefore, the PVR of MSA-P patients should be checked regularly using ultrasound sonography.[131,162] If repeated CIC is difficult to perform, CIC twice during the daytime and the use of an Intermittent Self Balloon Catheter (DIB International, Co. http://www.dib-cs.co.jp/products/urology/goods09/) during the night-time, is a choice that can be made by the patients/caregivers.