The Impact of Polypharmacy on Management of Lower Urinary Tract Symptoms in Parkinson's disease

Udit Saraf1, Amit Batla2, Ryuji Sakakibara3, Jalesh N Panicker4,5

Department of Neurology, Amrita Institute of Medical Sciences, Kochi, India

Department of Clinical and Movement Neuroscience, Faculty of Brain science, National Hospital for Neurology and Neurosurgery, Queen Square, London, United Kingdom

Department of Neurology, Sakura Medical Center, Toho University, Sakura, Japan

Department of Uro-Neurology, The National Hospital for Neurology and Neurosurgery, Queen Square, UCLH NHS Foundation Trust, London, United Kingdom

Department of Brain Repair and Rehabilitation, UCL Queen Square Institute of Neurology, Faculty of Brain Sciences, University College London, United Kingdom

ORCID ID: Udit Saraf: 0000-0002-8782-5472

ORCID ID: Amit Batla: 0000-0001-8952-2160

ORCID ID: Ryuji Sakakibara: 0000-0002-5803-169X

ORCID ID: J.N. Panicker: 0000-0001-5190-3259

Corresponding author-

Udit Saraf,

Department of Neurology, Amrita Institute of Medical Sciences, Kochi, India

Abstract:

Lower urinary tract (LUT) symptoms are a common presentation of autonomic dysfunction in Parkinson's disease. Symptoms significantly impact quality of life and are associated with worsening of motor symptoms and increased risk for falls. Different medical co-morbidities can often contribute to LUT symptoms, and a thorough evaluation therefore becomes essential. The effects of medications used for Parkinson's disease and other co-existing medical co-morbidities on LUT symptoms is often underestimated. Treatment options include behavioural therapy, oral agents such as antimuscarinic and beta-3 receptor agonist agents, botulinum toxin, and neuromodulation. The first line oral agents cause adverse effects that may exacerbate pre-existing Parkinson's disease-related symptoms. Furthermore, these oral agents can interact with other medications used in Parkinson's disease, and the challenges posed by interactions on pharmacological effects and metabolism are discussed. Knowledge about drug interactions can help in effective management of such patients and mitigate the risks for developing adverse effects.

Key points:

Lower urinary tract symptoms are common in patients with Parkinson's disease and have a negative impact on the quality of life.
A thorough evaluation is necessary and treatment should be individualised to ensure adherence, considering the impact of polypharmacy in elderly patients with PD. Bladder antimuscarinics are the mainstay of pharmacological management, but other pharmacological options are also available.

Botulinum toxin and neuromodulation are the other options available in challenging cases.

1. Introduction

Lower urinary tract (LUT) symptoms are a prominent manifestation of autonomic dysfunction in Parkinson's disease (PD). LUT symptoms significantly impact quality of life and are associated with an increased risk for falls and non-elective hospital admissions. The aim of this review is to outline the clinical presentation of LUT dysfunction in PD and to discuss the holistic approach to managing symptoms and its challenges.

2. Lower urinary tract symptoms

Parkinson's disease is characterised by motor dysfunction, predominantly bradykinesia, rigidity, gait impairment and tremor, however, is often associated with a range of non-motor features. The commonest of these is nocturia, reported in more than 50% of patients in most studies [1-3], though the prevalence was reported to be 35% in one study [4]. Lower urinary tract symptoms are commonly reported in 38-71% of patients with PD [5, 6]. Symptoms add a significant burden of care in PD and have a significant impact on health related quality of life [3]. Bladder problems, including urinary retention and urinary tract infections, belong to the top three causes for non-elective hospital admission of patients in the United Kingdom [7]. The presence of LUT symptoms is associated with an increased risk for falls [8], hip fractures [9], early institutionalization and increasing health-related costs [10].

Urinary storage symptoms arise from detrusor overactivity, which is reported in 45–93% of people with PD [11]. Urinary symptoms are reported to be associated with frontal lobe executive dysfunction, REM sleep behaviour disorder and a higher Hoehn & Yahr score [12]. The micturition reflex is under the influences of dopamine (inhibitory effect through the D1 receptor and facilitatory effect through the D2 receptor) and GABA (inhibitory) striatal dopamine activates the dopamine D1-GABAergic direct pathway which inhibits the micturition reflex via GABAergic collateral to the micturition circuit particularly to the periaqueductal grey matter (PAG). The disruption of the dopamine D1-GABAergic direct pathway and its GABAergic collateral to the micturition circuit in PD is thought to lead to the impairment of the micturition reflex and development of an overactive bladder (OAB) [13, 14]. Pathophysiologically, LUT symptoms correlate with degenerative changes seen in the striatum and other subcortical and cortical regions. LUT symptoms occurring early in the course of a Parkinsonian syndrome could be suggestive of multiple system atrophy (MSA) rather than PD [15]. LUT symptoms often precedes other non-motor and motor symptoms in MSA, and voiding dysfunction is commoner when compared to PD [16]. Post-void residual volume has been found to be greater in patients with MSA, and can be used to differentiate between MSA and PD [17]. LUT symptoms are commonly reported in patients with dementia with Lewy bodies, with nocturia and urinary urgency being the commonest symptoms [18, 19].

Patients with PD most commonly report urinary storage symptoms such as urinary urgency, and then bradykinesia and rigidity can slow the pace of reaching the toilet, culminating in incontinence episodes. Urinary frequency is increased in the daytime and at night, and nocturia (waking up from sleep 2 or more times a night to pass urine) has been shown to be associated with sleep disturbances, greater risk for falls and hip fractures, and higher mortality [9, 20-23]. Nocturia can occur due to OAB, but sleep disturbances can also result in nocturia when a patient with PD becomes aroused and aware of bladder sensations and decides to void. There is evidence to suggest that nocturnal polyuria, another reason for nocturia, characterised by increased night-time urine production, reflects an impaired circadian rhythm resulting in abnormally high volumes of urine being produced at night [24-

26]. Nocturnal polyuria is a medical condition and can result from obstructive sleep apnoea, loss of circadian pattern in blood pressure control (night-time dipping followed by morning surge coinciding with arousal), autonomic failure resulting in orthostatic hypotension and neurogenic supine hypertension, and concomitant medical disorders such as diabetes mellitus and congestive heart failure, and diuretic use [23].

Voiding difficulties are also reported, and these include delays in initiating urination (urinary hesitancy), prolonged/poor stream, and straining when voiding [14]. Urinary retention has been reported infrequently [27]. The severity of PD has been found to be a predictive factor for voiding dysfunction, irrespective of age or duration of illness [28]. In older men with PD, prostatic enlargement may contribute to LUT symptoms [15] including voiding symptoms. In men with benign prostatic enlargement, meticulous patient selection involving neurological and urological input prior to transurethral resection of the prostate can result in good outcomes [15, 29]. In older multiparous women with PD, pelvic floor weakness and associated stress incontinence might be mixed with other LUT symptoms. Bradykinesia of pelvic floor muscles causing "pseudo-dyssynergia" may be other key factors to consider in PD.

3.   Evaluation

The evaluation consists of history taking which can be supplemented using a bladder diary and questionnaires. Other urological and gynaecological conditions such as prostate enlargement, stress incontinence or pelvic organ prolapse can contribute to LUT symptoms and should be assessed. Systemic illnesses such as diabetes mellitus can also cause urinary dysfunction and should be considered.

A standard uro-neurological evaluation is performed for patients reporting LUT symptoms which includes urinalysis to exclude urinary tract infections and measuring the postvoid residual volume either by ultrasonography or in-out catheterization. Ultrasonography of the urinary tract and renal function tests help to evaluate the integrity of the upper urinary tract. Urodynamics testing, preferably with fluoroscopic imaging (videourodynamics), is useful to assess the extent of LUT storage and voiding dysfunction. Filling cystometry helps to assess bladder compliance and capacity and any detrusor overactivity.

Detrusor overactivity (DO) without significant post-void residual is the most common urodynamics finding in patients with PD and has been found to correlate with severity of motor impairment [30]. Evidence for mild urethral obstruction is seen in approximately half of patients with PD with voiding dysfunction on urodynamics findings [31]. Subclinical detrusor weakness during voiding can also be found on urodynamics [28].

4.   Management

4.1 Conservative approach

An individualised approach to managing LUT symptoms begins with conservative measures, maintaining an optimal fluid intake (1.5–2 L over 24 hours), avoiding beverages that may exacerbate urinary storage symptoms such as caffeinated and carbonated beverages along with alcohol, bladder training and pelvic floor muscle training [32]. Limiting fluid intake before bedtime may improve nocturia. Bladder diary self-monitoring helps to reduce symptoms, however, these should be part of a multicomponent behavioural therapy strategy to improve urinary symptom related bother and quality of life [33].

4.2 Pharmacological approach

Medications used for managing the symptoms of PD impact LUT symptoms. Functional urinary incontinence resulting from difficulties in reaching the bathroom on time due to Parkinson's-related slowness and gait mobility improves when motor symptoms of PD are treated [34]. Levodopa however may have a direct effect of modulating the micturition reflex. In drug naïve patients with PD, acute dosing with levodopa has been shown to worsen bladder function as per urodynamic parameters – detrusor overactivity threshold and bladder capacity, whereas chronic use over 2 months was associated with an improvement in the same parameters [35]. A significant improvement in nocturia has been demonstrated in an observational study of patients administered extended-release levodopa preparation at bedtime [36]. Safinamide, a monoamine oxidase-B inhibitor, was found to improve urinary urgency, incontinence, frequency and nocturia in a retrospective analysis of patients with PD on safinamide for managing motor symptoms [37]. Amantadine has also been shown to ameliorate nocturia and urinary urgency in patients with PD [38].

The M2 and M3 muscarinic receptors are the primary receptors involved in the cholinergic pathways modulating lower urinary tract functions in health, and antimuscarinic medications are the mainstay of pharmacological treatment for managing OAB symptoms. Solifenacin has been evaluated in PD in a randomised-control trial and though the frequency of micturition did not improve, number of incontinence episodes decrease significantly. In the open label phase of the trial, significant improvement in incontinence episodes, nocturia and patient perception of bladder function were observed [39]. Smaller open label observational studies in PD have demonstrated significant improvements in urinary frequency and urgency with other antimuscarinic agents, namely tolterodine [40] and oxybutynin [41]. Adverse effects arise from blocking muscarinic receptors at other sites and include blurred vision, dry mouth, constipation and acute cognitive changes that include developing confusion and hallucinations [42, 43]. Antimuscarinic agents can impair gut motility, thereby interfering with the absorption of drugs such as levodopa [43, 44]. They should be avoided in patients with narrow angle glaucoma or with severe constipation. Impaired sudomotor functions is reported in PD with autonomic dysfunction [45], and a case of hyperthermia following exposure to oxybutynin has been reported which may have occurred because of impaired thermoregulation due to its antiperspirant action [46].

β3-Adrenoceptor agonists have emerged as a safe and effective option for overactive bladder and mirabegron has been evaluated in PD. A recent randomised controlled study evaluating mirabegron in PD demonstrated significant improvements in mean micturition volumes when compared with behavioural therapy alone [47]. The mirabegron cohort demonstrated a reduction in the frequency, number, and severity of urgency episodes, number of incontinence episodes and increase in dry rate, but no reduction in nocturia episodes. In another randomised controlled study evaluating mirabegron in patients > 65 years with OAB, significant efficacy and safety was demonstrated and there was no worsening of cognitive function over 12-week follow-up [48]. Possible side-effects of this medication include worsening of palpitations, urinary retention and worsening of pre-existing hypertension.

Desmopressin, a synthetic analogue of vasopressin, has been shown to reduce nocturnal polyuria in PD when used as a single bedtime dose [49]. One of the concerns about using desmopressin is the risk for developing hyponatremia, which is greater in older patients, females, and those with medical co-morbidities [50]. If undetected, hyponatremia can present with nausea, vomiting, headache, and if uncorrected, can lead to seizures, altered sensorium. Hyponatremia can also lead to a worsening of motor symptoms.

The mechanisms underpinning nocturia is still unclear, but impaired circadian rhythm has been found to have a role in its pathogenesis [25]. Exogenous melatonin is known to help circadian function and an open-label clinical trial of sustained-release melatonin in patients with PD demonstrated beneficial effects with significant improvements in number of episodes of nocturia per night and related bother and average nocturnal voided volumes [24]. Melatonin has been used in PD patients to manage insomnia [51], and reduces nocturia by improving sleep efficiency as well.

Intradetrusor botulinum toxin is a licensed treatment for managing neurogenic detrusor overactivity and works by interfering with cholinergic and non-cholinergic mediated pathways in the bladder wall. The toxin also reduces P2X3 and TRPV1 expression in the suburothelial C-fibers of the human bladder through retrograde axonal transport [52]. A few open label studies have demonstrated botulinum toxin to be effective for managing detrusor overactivity in PD [53-57]. However, detrusor contractility is affected and increases the risk for developing urinary retention which, if substantial, would render patients temporarily catheter reliant till the effects of the toxin wears off.

Neuromodulation is an emerging non-invasive treatment for managing PD-related overactive bladder symptoms. Percutaneous tibial nerve stimulation is an effective option for managing overactive bladder symptoms and does not exacerbate the voiding dysfunction or increase post-void residue (PVR). A recent study with a tapering protocol showed significant improvement in both voiding and urodynamic parameters over 24 months [58]. Transcutaneous tibial nerve stimulation has also been trialled in patients with Parkinson's disease. Studies have shown significant improvement of symptoms in stimulation patients as compared with sham patients [59-61]. Sacral neuromodulation is an effective treatment for urinary storage and in a retrospective study more than 2/3rd of the patients with PD were able to discontinue medications for overactive bladder symptoms after sacral neuromodulation [62].

5. The challenges posed by polypharmacy

Overactive bladder symptoms in PD should be viewed in the wider context of concomitant medical co-morbidities [63, 64], with a national study reporting presence of psychiatric co-morbidity in >50% and somatic co-morbidity in >90% of patients with PD [65] (Table 1). Polypharmacy and hyperpolypharmacy is highly prevalent, being reported in 40% and 18%, respectively, of older adults with PD [66], and increases the risk for developing drug-related adverse effects.

5.1 Pharmacokinetic challenges

Understanding drug pharmacokinetics allows tailoring treatments and individualizing the therapeutic plans to improve efficacy, adherence and compliance to therapies. Extended-release oral formulations modify the proportion of parent drug and active metabolites in the blood and may improve adherence because of convenience of administration and better tolerability [67]. A medical records study found that patients on immediate-release oxybutynin were more likely to discontinue medications as compared to patients on tolterodine, trospium, solifenacin, darifenacin, and extended-release oxybutynin[68]. Lower incidence of central nervous system side-effects has been reported with the use of transdermal formulations of oxybutynin [69].

Another challenge posed by polypharmacy is the interaction between drugs that interfere with drug metabolism and excretion which is independent of anticholinergic properties. Isozymes of the cytochrome P450 system, mainly the CYP3A4 and CYP2D6 isozymes, are responsible for most of the drug metabolism through the liver [67]. Some drugs can modulate the activity of these enzymes- enzyme inducers lower plasma concentration of antimuscarinic drugs thereby reducing their efficacy, whereas enzyme inhibitors increase the plasma concentration of antimuscarinic drugs and thereby increase the risk of adverse effects. Mirabegron and most of the antimuscarinic agents are metabolised by the cytochrome P450 and therefore drug interactions are possible. Mirabegron is a moderate CYP2D6 inhibitor and can interact with other medications metabolised by CYP2D6 [70]. The different drug interactions involving cytochrome P450 system are outlined in Table 2.

Trospium chloride is unique amongst the antimuscarinic agents. This quaternary ammonium compound is excreted renally and therefore drugs that are eliminated by active renal tubular secretion can affect the metabolism of trospium. These include quinine, morphine, procaine, amiloride, triamterene, penicillin and other beta-lactams, salicylic acid, indomethacin, probenecid, thiazides, and ACE inhibitors [67].

5.2 Pharmacodynamic challenges

Anticholinergic adverse effects become more pronounced in the setting of polypharmacy. Patients with PD are exposed to different medications with anticholinergic properties, both for PD and non-PD indications. Central anticholinergics such as trihexyphenidyl are commonly used in PD for managing tremor and rigidity. Atypical antipsychotic agents such as quetiapine used to manage behavioural symptoms in PD have anticholinergic properties and therefore increases the anticholinergic burden [71]. Oral hypoglycemic agents, antidepressants (mainly tricyclic antidepressants) and β-blockers used for managing medical co-morbidities in PD also contribute to the anticholinergic burden, albeit to a lesser degree. Different scales have been developed that quantify the cumulative anticholinergic effects of drugs and different criteria are used to measure anticholinergic activity which can include average daily dose and cumulative dosage, serum concentration and clinical cognitive decline [72]. All the scales rate anticholinergic agents used for managing OAB symptoms in the highest category in terms of anticholinergic burden [73]. The results from different studies suggest that more than 50% of patients with PD have exposure to significant anticholinergic burden [74]. Therefore, there is a concern about using antimuscarinic agents for bladder management in this at-risk population.

Cognitive issues arising from using agents with anticholinergic properties has been recognised in recent years [75], and the use of anticholinergic medications amongst patients with OAB symptoms has been shown to be associated with a greater risk for developing new-onset dementia compared to beta-3 agonist users in a large population-based cohort [76]. Antimuscarinic agents interfere with cognitive functions through antagonism of the M1 receptor in the hippocampus, and to an extent M2 and M4 receptors, and a reduction in the number of cholinergic receptors with aging increases the risks for developing cognitive adverse effects [77, 78]. The cumulative anticholinergic burden has been reported to be the strongest predictor for not only cognitive impairment but also freezing of gait, leading to increased risk for falls, hospitalization and mortality [79]. A recent meta-analysis, however, did not show a significant cognitive decline in older adults without cognitive impairment or neurological disease taking anticholinergic agents over a long period [80, 81]. Baseline cognitive assessment before starting antimuscarinic agent, with serial follow-up monitoring, may help in early detection of cognitive adverse effects in patients at-risk for developing cognitive impairment [80].

Patients with PD may often be started on acetylcholinesterase inhibitors (AchEI) for managing cognitive impairment. Increased cholinergic activity in the LUT increases urinary urgency and incontinence and a progression of symptoms can sometimes be misinterpreted as disease progression. A population-based study found that patients with dementia who received AchEI had an increased risk of subsequently receiving an antimuscarinic agent for OAB symptoms, suggesting a prescribing cascade[82]. Starting an antimuscarinic agent to treat these OAB symptoms can interact with central M1-receptors resulting in a rapid deterioration of memory and cognition, however which is reversible[83]. To the contrary, a recent study in patients with Alzheimer's disease did not find significant association of urinary incontinence with cholinesterase inhibitor use, although worsening cognition was associated with increased incontinence[84]. The difference in findings was partly attributed to the relatively reduced use of AchEI in the study population. Another option in PD patients with LUT dysfunction is to prescribe a non-AchEI drug such as memantine for their cognitive impairment.

5.3 Managing polypharmacy

Patients with newly diagnosed PD on polypharmacy were found to have significantly lower cognitive scores than those not on polypharmacy[85], but conflicting reports have questioned such conclusion [86]. In patients with multiple comorbidities, it is prudent to review prescriptions to assess possible pharmacokinetic and pharmacodynamic interactions. Patients with PD present with several motor and non-motor symptoms and therefore it is prudent to prioritise symptom management in terms of impact on health and quality of life.

Deprescribing non-selective anticholinergic drugs is now the most effective intervention in PD patients [87]. Specific interventions for managing OAB symptoms in a cohort at risk for developing cognitive impairment such as PD starts with conservative measures, and if pharmacological agents are required, beta-3 receptor agonists [80]. If antimuscarinic agents are however indicated, penetrance across the blood-brain barrier is an important consideration. Different factors such as older age and conditions such as diabetes, neurological disease and stress can influence passive permeability and active transport mechanisms across the blood-brain barrier [88, 89]. Trospium chloride has been shown to have lower central nervous system penetrance because of its physicochemical properties as compared to tertiary amine antimuscarinic agents such as oxybutynin, solifenacin and tolterodine [90] and should be considered [91]. Another consideration is using an agent with less affinity for the M1 receptors in the CNS compared to the M3 receptor which is functionally more relevant to LUT functions such as darifenacin [80, 92, 93]. On-demand usage of an antimuscarinic is another approach and a randomised-controlled trial with fesoterodine demonstrated similar efficacy in on-demand group as compared to continuous usage group in terms of OAB scores with fewer adverse events such as dry mouth and constipation [94], however the cohort did not include patients with PD. Tibial nerve stimulation and botulinum toxin are other alternatives.

6. Conclusion:

LUT dysfunction is common in PD and management is challenging particularly in the elderly. Different conservative and pharmacological approaches to management and treatment options must be tailored to fit an individual patient, to ensure compliance and to

minimize adverse effects. Polypharmacy poses different issues, both pharmacokinetic and pharmacodynamic, and can lead to serious adverse effects including exacerbation of PD-related symptoms. The challenge for the clinician is to establish a treatment plan that optimises OAB management and improves quality of life however mitigates the risk posed by polypharmacy.

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Table 1. Challenges posed by polypharmacy

Pharmacokinetic
Immediate release and extended release formulations
Central nervous system penetration
Drug metabolism – cytochrome P450 system
Drug excretion – competing with other drugs for renal clearance
Pharmacodynamic
Cumulative anticholinergic burden
Interaction with cholinesterase inhibitors - prescription cascade
Reduced gut motility affecting drug absorption
Receptor selectivity

Table 2. Potential interactions of drugs used for managing OAB symptoms through cytochrome P450 system

Oral agents	CYP interaction[62]	Clinical consequences of drug interactions
Antimuscarinics		
Oxybutynin	CYP3A4	CYP3A4 inducers-phenytoin, carbamazepine, phenobarbitone, rifampicin-reduce levels CYP3A4 inhibitors-protease inhibitors, ketoconazole, macrolides, amiodarone- increase levels
Solifenacin	CYP3A4	CYP3A4 inducers-phenytoin, carbamazepine, phenobarbitone, rifampicin-reduce levels CYP3A4 inhibitors-protease inhibitors, ketoconazole, macrolides, amiodarone- increase levels
Tolterodine	CYP3A4, CYP2D6	CYP3A4 inducers-phenytoin, carbamazepine, phenobaribitone, rifampicin-reduce levels CYP3A4 inhibitors-protease inhibitors, ketoconazole, macrolides, amiodarone- increase levels CYP2D6 inhibitors- mirabegron, bupropion, fluoxetine, paroxetine, darifenacin-increase levels
Fesoterodine	CYP3A4, CYP2D6	CYP3A4 inducers-phenytoin, carbamazepine, phenobaribitone, rifampicin-reduce levels CYP3A4 inhibitors-protease inhibitors, ketoconazole, macrolides, amiodarone- increase levels CYP2D6 inhibitors- mirabegron, bupropion, fluoxetine, paroxetine, darifenacin-increase levels
Darifenacin	CYP3A4, CYP2D6	CYP3A4 inducers-phenytoin, carbamazepine, phenobaribitone, rifampicin-reduce levels CYP3A4 inhibitors-protease inhibitors, ketoconazole, macrolides, amiodarone- increase levels CYP2D6 inhibitors- mirabegron, bupropion, fluoxetine, paroxetine, darifenacin-increase levels
Beta-3 adrenergic agonist		
Mirabegron	CYP2D6	Increases levels of digoxin, warfarin, metoprolol, desipramine, thioridazine, flecainide, antimuscarinics metabolised by CYP2D6
Vibegron	CYP3A4	Avoid with CYP3A4 inhibitors and inducers Increases digoxin concentration- monitoring required