

## Review Article



# Relationship between Lower Urinary Tract Dysfunction and Dementia

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## ABSTRACT

Lower urinary tract dysfunction (LUTD) is a common health challenge in dementia patients with significant morbidity and socioeconomic burden. It often causes lower urinary tract (LUT) symptoms, restricts activities of daily life, and impairs quality of life. Among several LUT symptoms, urinary incontinence (UI) is the most prominent storage symptom in the later stages of dementia. UI in patients with dementia results not only from cognitive impairment, but also from urological defects such as detrusor overactivity. Management of LUTD in patients with dementia is based on multiple factors, including cognitive state, functional impairment, concurrent comorbidities, polypharmacy and urologic condition. Behavioral therapy under caregiver support represents appropriate treatment strategy for UI in these patients. Pharmacological treatment can be considered in patients refractory to behavioral therapy, but it is more effective when combined with behavioral therapy. Antimuscarinics and mirabegron, a beta-3 receptor agonist, are effective for managing storage symptoms involving the LUT. However, anticholinergic side effects in elderly subjects are a concern, particularly when there is a risk of exacerbating cognitive impairment with prolonged use of antimuscarinics. Proper recognition and treatment of LUTD in dementia can improve quality of life in these patients.

**Keywords:** Urinary Bladder; Lower Urinary Tract Symptoms; Urinary Incontinence; Dementia; Overactive Urinary Bladder; Underactive Urinary Bladder

## INTRODUCTION

The proportion of the elderly population has increased rapidly along with the increase in average lifespan. The prevalence of dementia, which is a typical disease associated with aging, also increases rapidly. Patients with dementia often suffer from urinary incontinence (UI), which is one of the lower urinary tract symptoms (LUTS), which continue to increase with advanced age of the elderly population. UI affects the quality of life in patients with dementia, resulting in medical morbidity, impaired self-esteem, early institutionalization in long-term care facilities, stress for families and caregivers, and substantial financial burden.<sup>1</sup>

Neurogenic lower urinary tract dysfunction (LUTD) refers to abnormal function of the bladder and urethra in the context of clinically confirmed relevant neurologic disorder.<sup>2</sup>

LUTD causes LUTS and is a major subgroup of broad LUTS due to the severity of symptoms and the broader implications of urinary dysfunction for health.<sup>2,3</sup> The normal bladder micturition cycle is composed of 2 phases: storage and voiding. During the storage phase, the bladder is passively filled with urine, whereas voiding is accomplished by contracting the detrusor muscle of bladder. The switch of lower urinary tract (LUT) function between storage and voiding is mediated by a long-loop spinobulbospinal micturition reflex involving the pontine micturition center (PMC) in the rostral brainstem.<sup>4</sup> During the storage, the afferent signals to the bladder increase in strength until they exceed a specific threshold in the brainstem, specifically the periaqueductal gray. In the absence of any controlling factors, the micturition reflex is triggered, i.e., the PMC is activated, the urethral sphincter relaxes, the bladder contracts, and voiding begins.<sup>4</sup> Urine storage restarts when the bladder is fully empty.

LUTD may involve either urinary storage or voiding. Storage symptoms include urinary frequency, urgency, nocturia, and UI, whereas voiding symptoms include weak stream, hesitancy, straining, double voiding, sensation of incomplete emptying and urinary retention. The pattern of LUTS and LUTD is influenced by the lesion distribution in the neuroaxis.<sup>5</sup> In particular, lesions of the subcortical white matter, brain stem, and white matter in the spinal cord affect neural networks controlling LUT function, leading to neurogenic detrusor overactivity (DO).<sup>5</sup>

## CHARACTERISTICS OF LUTD IN PATIENTS WITH DEMENTIA

### UI

UI is secondary to dementia and is most frequently associated with it in patients with LUTD because of similar underlying etiology and comorbidity.<sup>6</sup> According to the International Continence Society, UI is defined as a "complaint of involuntary loss of urine".<sup>7</sup> The frequency of UI gradually increases with age. It is classified into 3 types depending on the cause: urgency, stress and overflow. Urgency incontinence associated with urgency symptoms is relatively common in the elderly population.<sup>8</sup> Urgency incontinence is closely related to DO, and is caused by damage to the cerebral connecting pathways or dysfunction of the subcortical control circuit that suppresses spinobulbospinal micturition reflex.<sup>4</sup>

Among neurodegenerative diseases, neurodegeneration in the nigrostriatal dopamine system leads to disinhibition of the micturition reflex resulting in DO in Parkinson's disease (PD) and dementia with Lewy bodies (DLB).<sup>9</sup> However, in Alzheimer's disease (AD), lesions in the cholinergic pathway that originate from the Ch4 cell group of the nucleus basalis of Meynert in the medial frontal lobe result in DO, which suggests that cortical cholinergic neurons play an inhibitory role in the micturition reflex.<sup>8,10</sup> DO is observed in 92% of the patients with DLB and in 40% with AD, which can be a major cause of UI.<sup>9</sup> However, patients with vascular dementia manifest various aspects of UI depending on the region of brain damage.<sup>1</sup>

UI that is not caused by LUT is characterized by functional incontinence, which occurs when it is not possible to reach the toilet in time due to impaired cognitive activity, or lack of sufficient number of attempts. In patients with dementia, difficulty accessing the toilet, abnormal physical activity, and psychological factors can exacerbate existing UI. Functional incontinence occurs relatively early, especially in the case of vascular dementia, DLB, normal pressure hydrocephalus and fronto-temporal dementia, whereas in AD and PD with dementia, functional incontinence occurs after the disease has progressed considerably.<sup>9,11,12</sup>

### Underactive bladder

Among degenerative neurological diseases, detrusor underactivity (DU) is typically observed in PD, multisystem atrophy (MSA), multiple sclerosis and Guillain-Barre syndrome.<sup>13</sup> Patients with DU experience decreased sensation when the bladder is full, and incomplete voiding results in prolonged urination with insufficient detrusor contraction.<sup>13</sup> Among patients with PD, the most prominent LUTD was DO in 79% of cases, which was independent of disease severity.<sup>6</sup> The basal ganglia, including the substantia nigra, show an inhibitory effect on the micturition reflex. Therefore, dopaminergic neuron degeneration of the substantia nigra may promote DO. However, it has been reported that DU also occurs in approximately 16% of patients with PD.<sup>6</sup> In MSA and autonomic neuropathy, direct neuronal injury disrupts the efferent nerves, which may result in reduced neuromuscular activation that may manifest as an absent or poor detrusor contraction.<sup>13</sup>

## PREVALENCE OF LUTD IN PATIENTS WITH DEMENTIA

Most studies investigating the prevalence of LUTD in dementia have relied on both patient and caregiver reports. Among them, only UI has been the focus of most investigators.<sup>10</sup> The prevalence of UI in these studies can vary considerably from 11% to 93% in individuals with dementia, which may be attributed to differences in patient selection.<sup>1,10</sup> Among elderly subjects with dementia, the prevalence was higher, with 22% of community-dwelling elderly and 84% of nursing home residents reporting UI.<sup>14</sup> According to the data from South Korea, Na et al.<sup>15</sup> reported that the prevalence in patients with AD was 24.8%, and the 2 most common types included urgency incontinence (44.3%) and functional incontinence (25.3%).

Ouslander et al.<sup>16</sup> reported that 65% of subjects with UI experienced less than 3 episodes per week, 11% reported 3 to 6 episodes per week, and 24% had UI more than once a day. McLaren et al.<sup>17</sup> found that 90% of incontinent subjects reported at least 1 episode during the 3-week evaluation period, 78% experienced 1 weekly episode, and 40% had once-a-day incontinence. When these studies were combined, more than two-thirds of incontinent patients with dementia experience at least 1 episode per week. This finding contrasts with the study of general elderly population in which nearly 5% of the elderly had at least once a week UI.<sup>18</sup>

## EVAUATION

The evaluation of dementia patients with LUTD should be based on multiple factors that affect LUT function and adjusted for the diagnostic method according to the individual characteristics and the purpose of treatment. Diagnosis of dementia is usually made by a neurologist, but patients with LUTS at the urology department may show undiagnosed signs and symptoms of dementia. Therefore, close cooperation between neurologists and urologists is needed to assess and manage LUTS patients with dementia.<sup>12</sup> **Table 1** provides an overview of the essential evaluation of LUTD.

### History taking

Detailed medical history is the preliminary step in LUTD evaluation, as it provides essential information for understanding the cause and diagnosis, and enables therapeutic planning. The patient's fluid intake, micturition habits, and medications including anticholinergics and potential drug interactions should be carefully investigated. Polypharmacy is common in patients with dementia and chronic illness. However, medications taken for anxiety,

**Table 1.** Essential evaluation of lower urinary tract dysfunction

Methods	Details
Detailed history taking	Fluid intake Micturition habits Medications including anticholinergics
Questionnaires	International Prostate Symptom Score Overactive Bladder Symptom Score
Voiding diary	Time and volume of voiding Episodes of urinary incontinence and urgency
Physical examination	Abdomen, lumbar, pelvis and genitalia Bulbocavernosus reflex Anal reflex and anal sphincter tone
Urinalysis	Pyuria, bacteriuria, hematuria, glucosuria, ketonuria
PVR urine measurement	Ultrasonography (bladder scan) Catheterization

PVR: post-void residual.

depression and insomnia, may induce unexpected sedation, confusion and movement disorder, and thus are likely to induce functional incontinence.

Anticholinergic medications can induce voiding difficulties.<sup>12</sup> First generation antihistamines, tricyclic antidepressants, antipsychotics and anticholinergics used for allergies and respiratory diseases can lead to voiding difficulty and overflow incontinence due to urinary retention. In addition,  $\alpha$ -adrenoceptor agonist sympathomimetics used for suppressing intranasal hyperemia, especially used in otolaryngologic diseases, can severely exacerbate voiding symptoms in patients with bladder outlet obstruction, such as benign prostate hyperplasia. Narcotic analgesics used for analgesia can reduce the contractility of bladder, act on the central nervous system, and induce urinary retention and overflow incontinence.

Several validated questionnaires have been used to assess the LUTS in patients with LUTD. Above all, the International Prostate Symptom Score is commonly used and highly recommended for assessing the grade and severity of LUTS in women as well men. In addition, the Overactive Bladder Symptom Score comprising questions that address the 4 symptoms of overactive bladder is also recommended in patients with storage symptoms of LUTS.

The 3-day voiding diary, which records the time and volume of each voiding episode of incontinence and urgency, provides a real-time, objective, patient-reported measurement of LUTS, which might not be feasible via history taking or questionnaires.<sup>12</sup>

### Physical examination

Physical examination includes examination of the abdomen, lumbar regions, pelvis and genitals, and if necessary, genitourinary sensations, sacral reflexes, such as bulbocavernosus and anal reflexes, and anal sphincter tone.<sup>12</sup>

### Urinalysis

Urinalysis is essential to investigate pyuria and bacteriuria suggesting urinary tract infection, hematuria suggesting malignancy and glucosuria or ketonuria suggesting diabetes.<sup>19</sup>

### Post-void residual (PVR) urine measurement

The PVR urine volume can be measured with ultrasonography such as bladder scan or catheterization. An elevated PVR volume suggests voiding dysfunction. However, it cannot be used to identify whether this is caused by DU or bladder outlet obstruction.<sup>12</sup>

## TREATMENT

The patient care and surrounding care conditions should be evaluated for disease association and treatment planning. In addition, as mentioned in the 5th International Consultation on Incontinence, the expectations of both patients and caregivers, the nature of the proposed treatment, and the potential for benefits and harms should also be considered.<sup>1</sup> As the first-line treatment, non-pharmacological behavioral therapy is preferred. If behavioral therapy alone does not work, pharmacological treatment can be considered, but is more effective when the behavioral and pharmacological therapies are combined.

### Behavioral therapy

Behavioral therapy programs such as prompted voiding, timed voiding, and habit training can help reduce UI in the elderly living in nursing homes with limited physical and cognitive abilities. Pelvic floor muscle exercise, biofeedback and electrical stimulation therapy are recommended for elderly without advanced physical or cognitive dysfunction.<sup>20</sup>

#### *Prompted voiding*

Behavior toileting can be categorized into caregiver- and patient-dependent programs. Patients are regularly asked if toilet assistance is needed before an episode of UI occurs, but such assistance is provided only upon patient request.<sup>10,20</sup> According to the predetermined schedule, prompted voiding can be attempted in patients with impaired cognition. A family or a professional caregiver may ask the patient at regular time intervals (2 hours during the daytime and 4 hours at night) regarding the need to void and thereby provide assistance with the visit to the toilet. Even with dementia, it is desirable to preferentially use prompt voiding, if the patient is able to state his or her name and to distinguish between 2 objects. In addition, even in the case of a severely demented patient who has difficulty voiding regularly, it is possible to gradually improve UI by initiating prompt voiding.<sup>21,23</sup>

#### *Timed voiding and habit training*

Prompt voiding is induced by a caregiver, while timed voiding is regulated by the patients themselves to empty the bladder before UI occurs at the scheduled time. Timed voiding is useful for cognitively intact older adults with sensory impairment of the bladder due to neurological conditions. Habit training is a toileting program that matches patients' voiding habits or needs based on their voiding pattern. The goal is for the patient to follow a planned schedule that is shorter than the patient's normal voiding pattern, and is timed prior to a possible UI episode. Timed voiding and habit training are recommended for patients who can void independently.<sup>20</sup>

#### *Pelvic floor muscle exercise*

Pelvic floor muscle exercises are performed to increase the strength and duration of muscle contraction below the pelvis.<sup>24</sup> The principle is to intentionally contract the muscles to suppress the micturition reflex and increase the pressure of urethral closure to improve the urgency and urgency UI. Patients are educated on the methods for the contraction of pelvic floor muscles. The contract of the pelvic floor muscles suppresses detrusor contraction when urgency or UI is likely to occur. Patients are educated to contract the pelvic floor muscles for maximal strength and duration. Generally, patients tend to use other muscles, such as the rectus abdominis or gluteal muscles, instead of the pelvic floor muscles. Therefore, it is important to understand the use of muscles.<sup>20</sup> In general, the anus is tightened first as if lifting the anus with both legs stretched lightly, and the pelvic floor muscles are contracted, followed by relaxation of the

pelvic floor muscles. It is possible to increase the effect of exercise by steadily repeating multiple times, such as once in 30 minutes, twice a week, or more than 1 month. Even the elderly with mild cognitive impairment can be trained by expert instructors.<sup>25</sup>

*Biofeedback*

Biofeedback is based on measurements of intravaginal pressure or electromyography to enhance patient understanding of the pelvic floor muscles.<sup>12</sup> It is also an educational training that provides a strong motivation by directly evaluating the precision and repeatability of the pelvic floor muscle exercises. The therapeutic effect is enhanced when biofeedback is used together with pelvic floor muscle exercise.<sup>26</sup>

**Pharmacological treatment**

When behavioral therapy is not effective, drug treatment may be considered. The pharmacological treatment of LUTD in patients with dementia depends on whether the patient has storage (UI) or voiding (underactive bladder) problems. Storage incontinence can be alleviated with antimuscarinics (anticholinergics) and more recently, mirabegron, the first clinically available beta-3 receptor agonist, used either alone or as a combination.<sup>5,23</sup> Antimuscarinics suppress bladder contraction and mirabegron enables bladder relaxation.<sup>27</sup> However, the drug therapy for voiding problems involves only alpha-blockers currently, and there are no recommended medications for improving voiding and DU.<sup>5,11</sup> **Table 2** lists medications currently used in South Korea to treat storage symptoms such as UI.

*Antimuscarinics*

Antimuscarinics competitively inhibit the binding of acetylcholine to muscarinic receptors, resulting in suppression of involuntary contraction of detrusor muscle during the storage period and improved urgency and urgency incontinence.<sup>11</sup> Since the introduction of oxybutynin, several antimuscarinics such as oxybutynin, propiverine, trospium, tolterodine, fesoterodine, solifenacin and imidafenacin, have been marketed.<sup>12</sup> The M3 muscarinic receptor is widely distributed throughout the detrusor, urothelium, and suburothelium. However, antimuscarinics are associated with cognitive worsening, due to the blockade of M1 muscarinic receptor, especially in patients with dementia who have already reduced brain acetylcholine activity.<sup>1,19</sup> In general, antimuscarinic-induced cognitive impairment is reversible when antimuscarinic therapy is withdrawn. However, some studies suggest that antimuscarinics may be associated with an increased risk of dementia.<sup>1,28</sup> Among several

**Table 2.** Medications for urinary incontinence of lower urinary tract dysfunction available in South Korea

Drugs (trade name)	Dosage	Frequency	Comments
<b>Antimuscarinics</b>			
Oxybutynin (Ditropan)	5 mg	3 times daily	M1, M3, M4 selective, local anesthetic activity, calcium channel antagonistic activity, IR form may worsen cognitive function in older adults
Oxybutynin (Lyrinel XL)*	5 mg, 10 mg	Once daily	Long-acting preparation has fewer side effects than short-acting preparation
Propiverine (BUP-4)*	10 mg, 20 mg	Once daily	Nonselective, concurrent calcium channel antagonistic activity
Tolterodine (Detrusitol SR)*	2 mg, 4 mg	Once daily	Nonselective
Fesoterodine (Tobiaz)*	4 mg, 8 mg	Once daily	5-HMT, active metabolite
Solifenacin (Vesicare)*	5 mg, 10 mg	Once daily	Moderate M3 selectivity
Imidafenacin (Uritos)	0.1 mg	Twice daily	High M3 selectivity, short half-life
Trospium chloride (Spasmolyt)	20 mg	Twice daily	Quaternary ammonium compound, low propensity to cross the BBB, fewer cognitive side effects than other anticholinergics
<b>Beta-3 adrenergic receptor agonist</b>			
Mirabegron (Betmiga)*	50 mg	Once daily	Avoid anticholinergic adverse effects

M: muscarinic receptor, IR: immediate release, HMT: hydroxymethyl tolterodine, BBB: blood-brain barrier.

\*Controlled release.



antimuscarinics, oxybutynin has been shown to exhibit more significant adverse cognitive effects.<sup>1</sup> In contrast, trospium does not cross the blood-brain barrier. In any case, before prescribing the antimuscarinics, the patient's memory and cognitive functions should be evaluated for appropriate changes after treatment.

Acetylcholinesterase inhibitor (AChEI) treatment for dementia is associated with significant worsening of UI, because AChEI affects not only the central but also the peripheral nervous system.<sup>1,29,30</sup> This phenomenon is often misinterpreted as a sign of disease progression. Therefore, it would be more appropriate to reduce the dose of AChEI rather than add an antimuscarinic to treat dementia patients with UI due to the risk of cognitive decline and delirium.<sup>29</sup> When antimuscarinics are prescribed for patients with dementia who are already treated with AChEI, they cross the blood-brain barrier and bind the M1 muscarinic receptors in significant amounts leading to unexpected interactions and rapid deterioration in memory and cognition.<sup>1</sup>

Elderly people often consume multiple medications (polypharmacy), so it is necessary to accurately evaluate all medications prior to treatment.<sup>31</sup> Among the medications for chronic diseases, the components of anticholinergic drugs are often contained, so it is important to carefully determine and plan the total amount and duration of treatment with anticholinergic drugs. In the elderly, the cumulative use of anticholinergic medications is associated with increased risk of cognitive impairment.<sup>28</sup> Other common adverse effects resulting from the non-specific anticholinergic action include dry mouth and constipation.

PVR urine measurement should preferably be conducted before prescribing antimuscarinics. Because a large amount of acetylcholine is secreted during the bladder contraction at micturition, therapeutic doses of antimuscarinics do not affect PVR if the bladder contraction is normal. However, in elderly patients who have a weak detrusor function, there may be an increase in PVR or urinary retention.

#### *Mirabegron*

Mirabegron is the first drug approved as a beta-3 receptor agonist. It activates the beta-3 adrenergic receptors in the detrusor muscle, resulting in direct bladder relaxation and increased bladder capacity, resulting in similar therapeutic effect as existing antimuscarinics.<sup>19</sup> Its mechanism of action differs from that of antimuscarinics, and thus avoids the anticholinergic adverse effects in the elderly patients. Treatment with mirabegron over 12 weeks had no adverse impact on cognitive function in older patients at risk of or concerned with cognitive impairment, based on the Montreal Cognitive Assessment.<sup>32</sup> Therefore, mirabegron is increasingly being used as an alternative, especially to anticholinergic treatment in elderly patients.<sup>5</sup>

## CONCLUSION

LUTD in patients with dementia is a common and distressing condition and can have a significant impact on a patient's quality of life. The symptoms may increase the risk of falls and may lead to early institutionalization. The pathophysiology of LUTD is often multifactorial. Essential diagnostic evaluation includes history taking, physical examination, urinalysis and measurement of PVR urine volume. Management of LUTD in patients with dementia depends on multiple factors including the type of LUTS, the extent of cognitive and functional impairment and the patient's expectations. The first step in the treatment

is behavioral therapy, which includes prompted voiding, timed voiding, habit training, pelvic floor muscle exercise and biofeedback. Pharmacological treatment involves the use of anticholinergics and mirabegron, a beta-3 adrenergic receptor agonist. A careful risk-benefit analysis of medications is essential, especially during pharmacological treatment. Future studies are crucial to investigate the pathophysiology and treatment outcomes of LUTD in patients with dementia.

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