



## Review Article

# Current pharmacological and surgical treatment of underactive bladder

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### ABSTRACT

Underactive bladder (UAB) or detrusor underactivity (DU) is a common yet still poorly understood urological problem. In addition to true detrusor failure and neuropathy, the inhibitory effects of detrusor contraction by the striated urethral sphincter and the bladder neck through alpha-adrenergic activity may also play a role in the development of UAB or DU. Treatment of UAB or DU aims to reduce the postvoid residual (PVR) urine volume and increase voiding efficiency, either by spontaneous voiding or abdominal straining. Pharmacotherapy with parasympathomimetics or cholinesterase inhibitors might be tried, and benefits can be achieved in combination with alpha-blockers. Bladder outlet surgeries, including urethral onabotulinumtoxinA injection, transurethral incision of the bladder neck, and transurethral incision or resection of the prostate can effectively improve voiding efficiency and decrease the PVR in most patients with DU. The mechanisms have not been well elucidated. It is likely that ablation of the bladder neck or prostatic urethra might not only decrease bladder outlet resistance but also abolish the sympathetic hyperactivity which inhibits detrusor contractility in patients with idiopathic UAB or DU.

**KEYWORDS:** Bladder function, Detrusor underactivity, Medical treatment, Urinary retention

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## INTRODUCTION

Underactive bladder (UAB) or detrusor underactivity (DU) is a common urological problem in the elderly resulting in incomplete bladder emptying or chronic urinary retention. It causes impaired quality of life and is a threat to health as well [1]. The pathophysiology of UAB or DU may involve aging, bladder outlet obstruction, diabetes mellitus, and neurogenic etiology [2]. Patients with UAB or DU usually void with abdominal straining and large postvoid residual (PVR) urine is noted. Bladder sensation might also be impaired [3]. DU is also commonly seen in elderly patients with a weak general condition and multiple medical diseases, or after major surgery [4]. Some possible underlying pathogenesis for the development of transient DU have been postulated, including detrusor muscle damage, increased urethral afferent activity and neurological inhibition, and defective mucosal mechanoreceptors and chemoreceptors [5-7]. This article reviews the current treatment modalities for DU [Table 1].

## CURRENT MANAGEMENT OF UNDERACTIVE BLADDER

In clinical practice, patients with UAB or DU might have improvement of symptoms or regain spontaneous voiding after an indwelling catheter or after transurethral resection of the prostate (TURP). During the recovery period of one to 3 months, clean intermittent catheterization (CIC) or an indwelling Foley catheter or cystostomy for voiding training

is usually recommended. However, not all patients with UAB or DU can recover from difficult urination or chronic urinary retention in the short term. Patients who need CIC or an indwelling Foley catheter may have a low quality of life and emotional distress [8].

## PHARMACOTHERAPY FOR UNDERACTIVE BLADDER OR DETRUSOR UNDERACTIVITY

The treatment goal for UAB or DU is to relieve voiding difficulty, reduce PVR and prevent urinary tract infection or upper urinary tract deterioration. If possible, recovery of detrusor contractility to efficiently empty the bladder should be achieved. Otherwise, a decrease in bladder outlet resistance or increased cortical perception of bladder sensation may also improve voiding efficiency after treatment. However, medical treatment for UAB or DU has usually been disappointing. A recent review of systemic literature research failed to find effective treatment strategies for DU [9].

The efficacy of cholinergic drugs for reduction of the PVR in patients with UAB or DU is still controversial. Parasympathomimetic agents, such as bethanechol, have

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**Table 1: Current therapeutic modalities for underactive bladder**

Treatment	Mechanism of action	References
Indwelling Foley catheter	Continuous urine drainage per catheter	[8]
Trocar cystostomy	Continuous urine drainage per catheter	[8]
Parasympathomimetic or cholinergic drugs	Increase detrusor tonicity	[11,12,13,15]
Intravesical prostaglandin E2 instillation	Increase detrusor tonicity	[10]
Alpha-sympathetic blockers	Decrease bladder neck and urethral sphincter tonicity	[14,16]
Combined alpha-blockers and parasympathomimetics	Increase detrusor tonicity and decrease bladder neck and urethral sphincter tonicity	[14,17]
Transurethral resection of prostate	Decrease bladder outlet resistance Relief of inhibitory effect of sympathetic hyperactivity	[34,40,41,42]
Transurethral incision of bladder neck	Decrease bladder outlet resistance Relief of inhibitory effect of sympathetic hyperactivity	[31,32,33,35,36]
Urethral injection of onabotulinumtoxinA	Decrease urethral sphincter tonicity Relief of inhibitory effect of detrusor contractility	[21,22,23,24,25,27]
Electrostimulation	Stimulate pelvic nerve to facilitate detrusor contractions	[18,19]

been found to reduce the PVR at a dose of 50 mg four times daily in combination with intravesical instillation of prostaglandin E2 1.5 mg. However, the improvement was limited (PVR decreased from 426 mL to 325 L,  $P = 0.015$ ) compared with placebo [10]. Recent research does not support the clinical efficacy of bethanechol for DU [11,12]. Acetylcholinesterase inhibitors, such as distigmine bromide, have also been found to improve the maximum flow rate and detrusor pressure [13]. A combination of bethanechol chloride (60 mg/day) or distigmine bromide (15 mg/day) and an alpha-blocker is more effective than monotherapy for the treatment of voiding difficulty in patients with UAB [14]. Cholinesterase inhibitors might inhibit degradation of acetylcholine and provide beneficial effects for patients with UAB or DU. However, adverse events such as frequent defecation, fecal incontinence, diarrhea and frequent urination might bother patients [15]. Furthermore, these pharmacological treatments might not be suitable for patients with detrusor hyperactivity and inadequate contractility, in whom overactive symptoms are exacerbated after pharmacological treatment.

Decrease of bladder outlet resistance by medication has been considered effective to reduce the PVR and improve voiding efficiency and is widely prescribed for patients with UAB or DU. However, there have been few randomized control trials to prove the efficacy. One recent study demonstrated women with DU could have significant improvement in the International Prostate Symptom Score (IPSS), maximum flow rate (Qmax), PVR, and voiding efficiency after taking tamsulosin 0.2 mg daily [16]. Combination of an alpha-blocker with distigmine 5 mg daily was also found to improve the IPSS and quality of life index as well as reduce the PVR [16]. Combined silodosin and distigmine could increase voiding efficiency in Zucker diabetic fatty rats, a model of DU-like syndrome. Adding an alpha-blocker to an acetylcholinesterase inhibitor might result in additive efficacy [17]. In addition to pharmacological treatment, percutaneous tibial nerve stimulation and intravesical electrical stimulation have been shown effective for nonneurogenic, refractory lower urinary tract dysfunction in children [18,19].

### BOTULINUM TOXIN A URETHRAL INJECTION FOR UNDERACTIVE BLADDER OR DETRUSOR UNDERACTIVITY

The pathomechanism of UAB or DU is complex, including detrusor failure and a poorly relaxed or nonrelaxed urethral sphincter [6]. A spastic or poorly relaxed urethral sphincter is the main pathophysiology of dysfunctional voiding. It results in incomplete bladder emptying and might be one of the causes of DU [3,20]. Therefore, the urethra is an important therapeutic target in patients with DU.

Botulinum toxin A has been used for more than 10 years to treat adults with neurogenic or nonneurogenic voiding dysfunction due to a spastic or nonrelaxing urethral sphincter [21-23]. In patients with voiding dysfunction and urinary retention, indwelling catheters can be removed after urethral onabotulinumtoxinA injection [24]. Urethral onabotulinumtoxinA injection had been used to treat patients with DU and nonrelaxing urethral sphincter after radical hysterectomy [25]. In patients with DU due to cauda equina lesions, dysfunctional voiding, peripheral neuropathy and idiopathic etiologies, onabotulinumtoxinA at a dose of 50 U was effective in reducing the median voiding pressure ( $56.5 \pm 41.2$  vs.  $39.0 \pm 38.4$  cmH<sub>2</sub>O), maximal urethral closure pressure ( $65.5 \pm 38.1$  vs.  $50 \pm 32.1$  cmH<sub>2</sub>O), and PVR volume ( $300 \pm 189.1$  vs.  $50 \pm 153.6$  mL) at 2 weeks after treatment and the efficacy remained for 3 months [26]. In a study involving patients with low detrusor contractility, 48% (13 of 27) of patients who received an injection of onabotulinumtoxinA 50–100 U into the urethral sphincter showed improvement in detrusor contractility, indicating the neuromodulation effects between the urethral sphincter and bladder [27]. The therapeutic effects of botulinum toxin A on voiding dysfunction not only decrease urethral resistance by paralyzing the striated urethral sphincter but modulate detrusor contractility by eliminating the inhibitory effect of urethral afferent nerves on detrusor nucleus. For patients with DU, urethral sphincter onabotulinumtoxinA injection might result in a reduction in urethral resistance, which allows patients to void more easily with the aid of abdominal

pressure [24]. However, if the patient is weak and cannot generate adequate abdominal pressure to void, voiding difficulty, and a large PVR volume might persist.

Other causes of failed urethral botulinum toxin A treatment besides low abdominal pressure in patients with DU include a tight urethral sphincter, bladder neck obstruction, and psychological inhibition of voiding [28]. An open bladder neck is an important factor in patients who use abdominal pressure to passively overcome urethral resistance. If patients with DU cannot open the bladder neck by abdominal straining, urethral sphincter onabotulinumtoxinA injection might not be successful. Furthermore, as in patients with dysfunctional voiding, repeat urethral sphincter onabotulinumtoxinA 100 U injections in patients with DU might be necessary to achieve greater reduction of urethral resistance and facilitate abdominal straining to void [29].

### **TRANSURETHRAL INCISION OF THE BLADDER NECK FOR WOMEN WITH DETRUSOR UNDERACTIVITY**

Endoscopic bladder neck incision for patients with bladder neck dysfunction was first reported by Turner-Warwick in 1973 [30]. In Choudhury's study of the therapeutic effectiveness of transurethral incision of the bladder neck (TUI-BN) for women with bladder neck obstruction, the mean PVR decreased from 143 to 27 ml [31]. Jhang and Kuo had previously reported the short-term results in women with DU who received TUI-BN [32]. After the procedure, the PVR decreased by 56.3%, and 20 of 27 (74.1%) patients were free of CIC. Excellent results were reported in 14 (45.2%), moderate results in 11 (35.5%), and poor results in six (19.3%) patients after TUI-BN. A recent report of long-term follow-up after TUI-BN for women with DU showed an improved mean voiding efficiency and reduced PVR during a mean follow-up of 61.8 months. Multivariate analysis revealed that baseline intravesical pressure (Pves) was a significant predictor of successful results (OR = 1.024,  $P = 0.038$ ) [33]. Adequate deep incision of the bladder neck to the serosa layer is postulated to allow the bladder neck to remain wide open and reduce bladder outlet resistance during a long-term follow-up. A higher Pves at baseline predicted a satisfactory outcome, suggesting these patients can generate more powerful abdominal pressure to overcome decreased urethral resistance after TUI-BN compared with patients with a lower baseline Pves.

In normal micturition, the bladder neck can open to a funnel shape which facilitates urine flow through a nonobstructed outlet. Some women with DU can still urinate efficiently by abdominal straining because they can effectively open the bladder neck and relax the pelvic floor muscles during voiding. A nonopening bladder neck results in functional outlet obstruction during abdominal straining to urinate in women with DU. Therefore, ablating the anatomical structure of the bladder neck and reducing bladder outlet resistance are helpful in facilitating spontaneous urination by abdominal straining in these DU patients. After TUI-BN for women with DU, the mean voiding detrusor pressure significantly improved in some patients, especially in those with nonneurogenic DU. Fifteen of 19 male

patients (78.9%) with nonneurogenic noncontractile bladders also had significant return of detrusor contractility after holmium laser enucleation of the prostate [34]. Contractions of the urethral sphincter stimulate proprioceptive nerves in the bladder muscle, which then activate inhibitory neural control of bladder contraction [35,36]. The bladder neck and proximal urethra also play roles in the guarding reflex of the micturition cycle [35]. The greatest concentrations of nerves in the bladder neck are at the 4 and 8-o'clock positions [37]. TUI-BN can not only destroy the bladder neck structure but also damage neural innervation. Some patients with nonneurogenic DU may regain detrusor contractility after TUI-BN through disruption of the guarding reflex. For the other patients, TUI-BN reduces bladder outlet resistance and allows them to void using a lower abdominal straining force [33].

The adverse effects of TUI-BN in women include stress urinary incontinence in the daytime and overflow urinary incontinence during sleep. Preoperative urodynamic study to detect a low compliant bladder might alert the surgeon to the need for a less invasive TUI-BN. Augmentation enterocystoplasty might be needed to increase bladder volume before TUI-BN in patients with small, contracted bladders. Surgical complications include postoperative hemorrhage and inadvertent vesicovaginal fistula. The former can be avoided by meticulous hemostasis, the latter by careful inspection of tissue properties during TUI-BN, especially in women who have had radiotherapy for pelvic cancer.

### **TRANSURETHRAL RESECTION OF THE PROSTATE FOR MEN WITH DETRUSOR UNDERACTIVITY**

Bladder function and voiding efficiency may differ between patients with DU. According to the classification of Cucchi *et al.*, UAB/DU can be divided into: (1) low detrusor contraction velocity, low isovolumetric detrusor pressure, and voiding efficiency >67%, (2) low detrusor contraction velocity, low isovolumetric detrusor pressure and voiding efficiency 67% or greater, and (3) low maximum contraction velocity, normal isovolumetric detrusor pressure and voiding efficiency 67% or greater [38]. In men with UAB/DU with or without outlet obstruction, prostatic resistance may play an important role in voiding efficiency. A long-term follow-up urodynamic study reported that TURP may not always be effective in male patients with low detrusor contractility [39]. However, one study found that after TUR-P, the IPSS, quality of life index, and PVR were significantly improved in patients with nonobstructed and weak bladder contractility and all parameters improved in patients with obstructed and/or normal bladder contractility [40]. Another study also suggested that men with DU may still have a significantly improved Qmax and PVR after TURP [41].

Clinical experience also reveals that patients with chronic urinary retention may resume spontaneous voiding and normal detrusor contractility with time after appropriate treatment and bladder management. Therefore, various medical and surgical treatments including bladder outlet surgeries and urethral sphincter botulinum toxin A injection have been used to improve voiding efficiency based on clinical and urodynamic findings. Between 1998 and 2015, a total of 86 men with DU

were treated in our department. Among the 86 men, 38 of the 44 who had TURP (86.4%) and 9 of the 16 (56.2%) who had transurethral incision of the prostate (TUIP) regained spontaneous voiding without an indwelling catheter or CIC. Patients with bladder function recovery had significantly greater bladder compliance ( $79.1 \pm 108.8$  vs.  $38.3 \pm 51.5$ ,  $P = 0.024$ ) and higher detrusor pressure ( $6.44 \pm 7.59$  v  $3.65 \pm 3.3$ ,  $P = 0.02$ ) than those without recovery [42].

## RECOVERY OF BLADDER FUNCTION AFTER BLADDER OUTLET SURGERY

The bladder neck and prostatic urethra are innervated by the sympathetic adrenergic nerves. Ablation of the bladder neck and prostatic urethra might abolish the sympathetic hyperactivity which inhibits detrusor contractility. It is also possible that the inhibitory effect of adrenergic hyperactivity on detrusor contractility can be modulated after TUIP or TURP, resulting in a recovery of detrusor function that has been inhibited. We have previously performed TUI-BN to decrease the bladder outlet resistance in patients with UAB/DU [43]. Patients with idiopathic DU may regain adequate detrusor contractility and resume spontaneous voiding [32,43]. This phenomenon was observed not only in idiopathic DU but also in neurogenic DU, suggesting a micturition facilitating reflex might be triggered after TUI-BN [44]. TUI-BN was performed in 22 spinal cord injured patients with voiding dysfunction due to bladder neck dysfunction and detrusor sphincter dyssynergia. Detrusor pressure decreased significantly in 9 who had a high baseline voiding pressure and increased significantly in 13 who had impaired detrusor contractility [44]. Recent study also revealed that improved bladder voiding function can be achieved by TUI-BN in patients with bladder neck dysfunction and impaired detrusor contractility. Even in the patients with persistent DU, 67% could void adequately with the aid of abdominal straining [45].

Transurethral bladder outlet surgery, including TUI-BN, TUIP, and TURP, not only relieve bladder outlet resistance but also might reduce the inhibitory effect of detrusor contractility caused by alpha-adrenergic hyperactivity in the bladder neck and prostatic urethra [46], thus facilitating urination in male patients with idiopathic DU, either by spontaneous voiding or abdominal straining [47]. If DU remains after transurethral surgery, the lower urethral resistance provides a chance for patients to urinate by abdominal straining and most of them can resume spontaneous voiding without a catheter.

## CONCLUSION

UAB or DU is a common yet still poorly understood the urological problem. Treatment of UAB or DU aims to reduce the PVR and increase voiding efficiency. Pharmacotherapy with parasympathomimetics or cholinesterase inhibitors with or without alpha-blockers is the first line treatment. In failed cases, bladder outlet surgeries, including urethral onabotulinumtoxinA injection, TUI-BN, TUIP or TURP can effectively improve voiding efficiency and decrease the PVR in most patients with DU.

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## Conflicts of interest

There are no conflicts of interest.

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