



# New therapeutic directions to treat underactive bladder

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Underactive bladder (UAB) is a term used to describe a constellation of symptoms that is perceived by patients suggesting bladder hypocontractility. Urodynamic measurement that suggest decreased contractility of the bladder is termed detrusor underactivity (DUA). Regulatory approved specific management options with clinically proven ability to increase bladder contractility do not currently exist. While DUA specific treatments presumably will focus on methods to increase efficiency of bladder emptying capability relying on augmenting the motor pathway in the micturition reflex, other approaches include methods to augment the sensory (afferent) contribution to the micturition reflex which could result in increased detrusor contractility. Another method to induce more efficient bladder emptying could be to induce relaxation of the bladder outlet. Using cellular regenerative techniques, the detrusor smooth muscle can be targeted so the result is to increase detrusor smooth muscle function. In this review, we will cover areas of potential new therapies for DUA including: drug therapy, stem cells and regenerative therapies, neuromodulation, and urethral flow assist device. Paralleling development of new therapies, there also needs to be clinical studies performed that address how DUA relates to UAB.

**Keywords:** Detrusor underactivity; Future treatments; Underactive bladder

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## INTRODUCTION

The term “underactive bladder” (UAB) refers to “a symptom complex suggestive of detrusor underactivity and is usually characterized by prolonged urination time with or without a sensation of incomplete bladder emptying, usually with hesitancy, reduced sensation on filling, and a slow stream” according to the Underactive Bladder Foundation ([www.underactivebladder.org](http://www.underactivebladder.org)). The term “detrusor underactivity” (DUA) is a urodynamic diagnosis defined by the International Continence Society as a bladder contraction of reduced strength and/or duration resulting

in prolonged or incomplete emptying of the bladder [1]. In this paper, we will focus on potential treatments that could increase bladder contractility and/or increase bladder emptying efficiency. This review will suggest potential treatments of DUA based on biologic plausibility and/or published data, but it should be realized that treatments for decreased detrusor contractility may not necessarily equate to decreased UAB symptoms.

## DRUG THERAPY

Drug therapies should be developed based on pathophy-

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siologic mechanisms of DUA. For normal voiding and bladder emptying, the central nervous system, peripheral nervous system, and lower urinary tract (bladder, urethral sphincter, pelvic floor muscles) need to be intact and functioning normally. Understanding detrusor contractility mechanisms should form a foundation for discovering new targets for DUA. Detrusor smooth muscle contractility depends on intact efferent neural function, intact neuroeffector junction function, and intact postjunctional excitation-contraction coupling events. When the anatomy or function of any aspect of this system is altered and exceeds the system's ability to compensate, issues with voiding/bladder emptying and subsequent DUA will arise.

The earliest concept for a DUA treatment is a drug that increases or augments any part of the efferent (motor) limb of the micturition reflex. Most notably, a drug that works to augment the excitatory neurotransmitter (acetylcholine) actions at the detrusor neuroeffector junction would appear logically able to help alleviate DUA. These drugs include muscarinic agonists, such as bethanechol and carbachol, and cholinesterase inhibitors such as distigmine, pyridostigmine and neostigmine. Unfortunately, very few studies have shown efficacy of these agents in DUA. The level of evidence to support their clinical use especially when their side effects are taken into account is minimal [2]. These agents have undesirable side effects such as nausea, vomiting, diarrhea, visual impairment due to lack of accommodation, headaches, bronchospasms and even severe cardiovascular events. These side effects limit their use. A study from 15 years ago showed essentially no effect from patients taking bethanechol (a muscarinic agonist) [3].

Perhaps, discoveries for new pharmacologic agents that work outside of muscarinic agonism could come from studying clinical populations that have known DUA - the elderly population. In the aged bladder, there was a decrease in excitatory motor innervation [4] along with detrusor muscle loss and axonal degeneration [5,6]. It has been shown that aging results in increased ATP (adenosine triphosphate, a purinergic neurotransmitter) release by the neuroeffector junctional efferent nerves in the bladder [7]. The paradox of how increased ATP, which is an excitatory neurotransmitter for bladder contractility, might be causal in DUA was suggested by mouse experiments showing that ATP release by efferent nerves blocked the muscarinic activation required for bladder contractility [8]. However, it should be noted that ATP may not play much of a role in human detrusor contractions [9]. Therefore, the potential role of ATP in human DUA is complex and more nuanced. ATP has differing effects depending on the bladder location

of its activity. For example, ATP's activity in the urothelium and lamina propria (or mucosa of the bladder as part of urothelial-afferent signaling) may be more effective in promoting contraction, rather than ATP's activity within the detrusor compartment. This will be discussed later.

Another potential druggable target is detrusor smooth muscle potassium channels [10]. The most studied potassium channel has been the BK channel (large conductance, calcium activated, voltage gated potassium channel) [11]. The other names for the BK channel include hSlo and MaxiK. The clinical translatability of preclinical studies of BK channel biology has been cast in the light of treating overactive bladder (OAB). Whether these findings can be simply "reversed" in order to apply to DUA, since DUA can be thought as opposite of OAB, is unknown and remains to be tested. There are other potassium channels besides BK in the detrusor smooth muscle and focusing on one type of potassium channel to treat DUA may be insufficient. Even if the detrusor smooth muscle contraction can be amplified, this does not address the bladder outlet (urethra) which must be relaxed at time of detrusor contraction for efficient bladder emptying. Increasing bladder contraction without simultaneously decreasing urethral outlet resistance would not result in efficient emptying and may compromise upper urinary tract (kidney) integrity.

After detrusor smooth muscarinic receptor activation, downstream signaling events couple the excitation of the smooth muscle cell to the contractile apparatus within the cell (excitation-contraction coupling). These events depend on regulation of intracellular calcium concentration as the contractile proteins utilize calcium to generate force. Targets that could modify intracellular calcium could be used for DUA. However, because intracellular calcium is also critical in regulation of cardiovascular smooth muscle, finding bladder selectivity would be paramount to minimize cardiovascular side effects. Bladder selectivity has not been clearly demonstrated in the oral pharmacologic agents currently used to treat bladder disorders. Other proteins involved in excitation-contraction coupling include kinases and phosphatases. Most of these enzymatic proteins are also commonly expressed by other cells, thus increasing the side effect profile for drugs that target these enzymes.

Alpha-blockers are the most common clinically used drug for DUA currently. The proposed mechanism of action of alpha-blockers is relaxation of the smooth muscle within the bladder outlet (prostatic urethra in males, bladder neck/proximal urethra in females). It is uncertain if alpha-blockers can increase bladder contractility. A preclinical study of use of alpha-blockers in a spinal cord injury of

DUA has been published, but in this study, the alpha-blocker tamsulosin did not increase detrusor pressure [12]. The effect of tamsulosin on the bladder outlet was not measured and the effect of decreasing postvoid residual volume in this study may have been related to tamsulosin inducing a decrease in bladder outlet resistance.

The modulation of sensory afferent limb of the micturition reflex to impact bladder contraction has been less studied than modulating the motor efferent limb. DUA may not just reflect diminished motor outflow, but may also be caused by diminished sensory inflow to the micturition reflex [13]. In patients with DUA altered sensory protein expression, increased suburothelial inflammation were observed in bladder biopsies [5,6]. Investigators have also theorized that the motor efferent system can feedback directly on the sensory afferent system within the bladder wall (the so called “motor sensory system”), with the hypothesis that augmenting the sensory pathway can drive bladder contractions [14]. Therefore, pharmacologic targets that augment sensory input into the micturition reflex may be effective in increasing bladder contractility. Different bladder sensory related neurotransmitters have been studied including SP (substance P), ATP (adenosine triphosphate), and neurokinins. The neurotransmitters, along with their cognate receptors, can also be considered druggable targets.

Other cells that could be targeted by drug therapy include suburothelial myofibroblasts. These are specialized pacemaker cells within the lamina propria and can communicate with urothelial cells and the afferent nerve fibers. These cells can amplify sensory signals from the bladder [15] and possibly augment a detrusor contraction reflex. Another bladder compartment that could be a druggable target for DUA is the vasculature, specifically vasculature in the lamina propria. Using a rat model, investigators showed that progressive vascular damage may be responsible for pathogenesis of DUA [16]. Recent studies on potassium channel regulation of bladder vascular smooth muscle tone was published [17]. Prolonged dysregulation of bladder blood flow at the vascular smooth muscle level can be theorized to lead to DUA. The urothelium can also be targeted as the urothelium is part of the urothelial-afferent system [18] and also part of the “mucosal” unit (urothelium + lamina propria) [19]. A recent study of patients with DUA showed altered expressions of several urothelial proteins including P2X3 receptor, M2/M3 muscarinic receptors, E-cadherin and endothelial nitric oxide synthase [5]. Augmented urothelial release of ATP was seen in bladder hypersensory disorder of interstitial cystitis [20]. The released of ATP by the urothelium can interact with sensory nerve fibers the

lamina propria leading to triggering of the micturition reflex. Mice lacking the ATP receptor, P2X3, had areflexive and enlarged nonemptying bladders [21]. Recently, investigators showed that bladder urothelial ATP was decreased in men with DUA from bladder outlet obstruction [22]. ATP is also an excitatory neurotransmitter for detrusor smooth muscle contractions. However, as discussed above, ATP did not appear to play a role in normal human bladder detrusor contractions [9] and increased purinergic signaling suppressed normal muscarinic mediated bladder contractility mechanisms [8]. Nevertheless, ATP and its multiple receptors (purinergic signaling), if targeted in the proper bladder compartment, could be utilized in treating DUA.

Some investigators have proposed that DUA results from untreated or treatment refractory detrusor overactivity. Patients can present with both detrusor overactivity with impaired contractility suggesting a potential link between these two disorders. The presence of detrusor overactivity is not mutually exclusive of having DUA. It is thought that chronic detrusor overactivity results in impaired detrusor muscle fatigue or progressive ischemia, inflammation and oxidative damage, which can lead to detrusor underactivity [23].

Because a fibrosed bladder is less efficient in contraction and thus emptying the bladder, pharmacologic interventions to prevent or reverse bladder fibrosis could also be considered in treatment of DUA. While bladder fibrosis accompanies the aging bladder, bladder outlet obstruction can also lead to fibrosis and DUA. A recent review pondered the question of whether fibrosis, after it has occurred, can be reversed [24]. Bladder fibrosis occurred when there was supraphysiologic repetitive bladder strain that triggered downstream activation of pro-fibrotic pathways including transforming growth factor  $\beta$  (TGF $\beta$ ) and hypoxia inducible factor. Targeting these pathways to reduce or prevent bladder fibrosis may be possible, though reduction of any untoward bladder strain would be the initial approach as this removes the main stimulus for bladder fibrosis. Inflammation from lipopolysaccharides has been shown to lead to bladder fibrosis [25], suggesting that recurrent urinary tract infections could lead to changes in bladder compliance and/or contractility.

Prostaglandins are known to be involved in the modulation of bladder function in both the normal state and in pathological conditions [26]. Therefore, prostaglandin E2 (PGE2) has also been used in the treatment of DUA but with little improvement of symptoms [27,28]. Investigators showed prolonged benefits of intravesical PGE2 in patients who were already being treated with

oral cholinergic agonists [29]. However, a later randomized prospective study only showed modest benefit when PGE2 was used in combination with bethanechol over a placebo combination [30]. In patients whom the combination worked, the improvement was sustained at 6 months with the authors concluding that a trial of the combination could be warranted in certain patients with urine retention and or unwilling to use intermittent catheterization. The use of ONO-8055, a novel selective PGE2 and PGE3 receptor agonist in DUA in a rat lumbar spinal canal stenosis model resulted in decreased PVR urine, voiding pressure and bladder capacity. *In vitro*, ONO-8055 caused relaxation of urethral strips and contraction of bladder strips probably explaining the decrease in voiding pressure [31]. A selective approach to the use of prostaglandins might be a more successful approach in the use of prostaglandins in the treatment of DUA. In a monkey model, ONO-8055 improved voiding function further demonstrating the potential of ONO-8055 as a possible effective pharmacotherapy in DUA treatment [32].

The lack of estrogen by ovariectomies in a rodent model has been observed to result in diminished detrusor activity, detrusor muscle loss and impaired contractility [33-36]. Estrogen has also been shown to be a neuroprotectant [37]. Thus, the lack of estrogen can adversely affect the neuromuscular function of the bladder from both a neural and smooth muscle basis. Further studies of the role of estrogen in the pathogenesis of DUA are needed to further understand its potential role as a therapeutic agent.

## STEM CELLS AND REGENERATIVE THERAPY

The use of stem cells has been increasing in the recent years in the treatment of various diseases. Stem cells are divided into 2 types—embryonic and adult stem cells. Because of the ethical dilemmas in use of embryonic stem cells, research has focused on adult stem cells. Adult stem cells are located within hematopoietic niches (precursors for blood cells), bone marrow stroma (mesenchymal stem cells, MSC) or in various organs as precursor cells for that particular organ. Properties of stem cells, no matter the location, include capability of dividing and renewal for long periods, being unspecialized, yet with ability of being able to differentiate into specialized cells. Use of MSC in treating DUA has been studied. A study found that MSC expressed contractile proteins and behaved functionally similar to detrusor smooth muscle *in vitro*, suggesting that MSC can be used to regenerate detrusor smooth muscles

[38]. An *in vivo* DUA animal model (induced by bladder ischemia) was treated by intravascular MSC injection prior to ischemia with resulting maintenance of detrusor smooth muscle function after ischemia [39]. In another *in vivo* model, intradetrusor injection of MSC after partial bladder outlet obstruction prevented the development of DUA [40]. Soluble growth factors such as TGF- $\beta$ 1 and cell-cell adhesion molecule cadherin-11 have been shown to facilitate transformation of MSC to functional smooth muscle cells [41]. These findings build the foundation for further studies on use of MSC, possibly used in combination with various growth factors, to treat DUA.

Another approach to treating DUA is to use autologous muscle derived cells (ADMC) harvested from skeletal muscle and injected into the bladder to treat DUA as a regenerative approach. Investigators have demonstrated that injection of ADMC resulted in myotube formation in the smooth muscle layer of bladder walls of rats [42]. They suggested that injection of ADMC could enhance bladder contractility. Immunohistochemical characterization of these ADMC revealed presence of myofibroblasts, but also fibroblasts [43]. Intradetrusor injections of ADMC were performed in a 79-year-old patient with underactive bladder resulting in a decrease in maximum bladder volume and improved voiding at 1 year [44]. However, he still required occasional self-catheterization but reported no side effects such as hematuria, urgency, frequency nor infection related to the injections. While this is a promising first case of injection of ADMC in the treatment of DUA, increasing detrusor contractility will not affect the bladder outlet relaxation. Ideally, coordinated outlet relaxation should occur with bladder contractions to allow efficient emptying.

## GENE THERAPY

Injection of myoblasts, transformed by viral vectors, has been shown as a potential method for gene transfer to deliver therapeutic proteins into muscle in diseases such as Duchenne muscular dystrophy [45]. This method could be used to deliver genes that promote contractility of detrusor smooth muscles. Comparisons of efficiency of gene delivery between tissue injection, adenoviral infection and adenoviral transduced myoblast injection revealed that the myoblast injection was the most effective method of delivering the gene to the tissue [46]. Other forms of gene delivery involve using herpes simplex virus to delivery gene to the dorsal root ganglia which is part of the sensory afferent pathway. This method has been used to transfect the nerve growth factor (NGF) gene to the sensory ganglia cells innervating

the bladder as a treatment of diabetic cystopathy when NGF is diminished in the DRG [47]. This same approach can be contemplated in DUA where augmented sensory input into the sensory limb of the micturition reflex can result in increased bladder contractility.

## NEUROMODULATION

Pelvic physiotherapy is usually a first line for dysfunctional voiding but little is known about the effectiveness of pelvic physiotherapy in treating DUA. Small randomized clinical trials have shown that transcutaneous stimulation benefitted DUA in children [48]. The children with DUA enrolled in this trial had “lazy” bladders in which the child voided infrequently (~3 times a day), with high volumes (~400 mL), but the PVR was low (~70 mL). The symptom bother perceived by these children were not described. Though the investigators stated that urodynamics were performed in all subjects confirming DUA, there were no urodynamics data presented. The investigators found that after pelvic transcutaneous stimulation, voiding frequency increased, bladder capacity decreased, voiding time decreased, and PVR also decreased. In a rat model, direct stimulation of the pudendal nerve resulted in increased voiding efficiency in a diabetic DUA model [49].

A meta-analysis showed that sacral neuromodulation works in patients with nonobstructive urinary retention [50]. However, in many of these trials the main outcome is postvoid residual (PVR) volume or number of self-catheterization episodes in a day. Sacral neuromodulation has also been shown to improve the impaired contractility in patients with detrusor hyperreflexia impaired contractility [51]. More studies are needed to further identify patients who will have successful resolution of their symptoms after implantation of a permanent neuromodulation device [52].

The future for neuromodulation might include direct stimulation of different brain areas that are involved in voiding. Male mice void based on social rank with the male dominant mouse voiding frequently and the nondominant mice voiding much less frequently as if they had detrusor underactivity or DUA [53,54]. The DUA voiding behavior of the nondominant male mouse could be altered by triggering areas of the brain to make these nondominant mouse void as if it were a dominant mouse [55]. These data suggest that stimulation of certain loci in brain can lead to augmented voiding behavior. Transcranial stimulation, whether with magnetic or other electrical energy, has been used to treat a variety of functional disorders such as depression, anxiety, tinnitus, poststroke aphasia, movement disorders, and even

addiction. It is conceivable that transcranial stimulation may be used to induce voiding or increase bladder contractility during voiding.

A closed-loop feedback neuromodulation system is a system that involves implantation of engineered electronic prosthetic devices that can monitor as well as stimulate both afferent and efferent pathways within the lower urinary tract and/or the central nervous system. The monitoring and stimulation is completely automated and constantly occurring throughout time (dynamic) such that the patient does not have to provide any input to the system. This closed-loop feedback system is intended to mimic normal storage and emptying of urine through modulation of both sensory and motor pathways of the micturition reflex. An animal model proof of concept was tested in which monitoring of bladder filling was measured by electrical currents triggered by bladder filling. These electric signals from bladder filling was then used to feedback to initiate pudendal nerve stimulation [56]. As discussed above, pudendal nerve stimulation can augment bladder emptying in a diabetic DUA rat model [49], but pudendal nerve stimulation at different parameters can also increase bladder storage capability [57]. The closed-loop feedback systems are designed with the neurogenic bladder in mind because, often, the neurogenic bladder has both storage and emptying problems. However, it is quite possible to have a simpler closed-loop design for use in DUA.

## URETHRAL FLOW ASSIST DEVICE

In 2014, the U.S. Food and Drug Administration (FDA) approved a nonsurgically inserted urethral device in females to assist with bladder drainage for those with urinary retention due to DUA (InFlow Intraurethral Valve-Pump, Vesiflo, Redmond, WA). The device is inserted and left indwelling in the urethra for a period up to 30 days. It is anchored in place by silicone tines that are deployed at the bladder neck during insertion. For removal, the device is pulled out with gentle outward force which collapses the silicone tines and allows the device to come out and be exchanged for a new device.

The patient turns on the pump within the InFlow with a remote control when she wants to void. With the pump on, urine is pumped out of the bladder, through the InFlow and out the urethral meatus. This creates a flow similar urinary flow as volitional voiding.

There have been no published studies on the use of the InFlow. The risks would be like having an indwelling urethral catheter since both are foreign body within the

lower urinary tract connected to the external environment. These risks include urinary tract infection, bladder stones, urethral erosion and development of a patulous urethra. Long-term use of this device may also result in the rare development of squamous cell carcinoma from chronic foreign body in the lower urinary tract. Therefore, this device is likely best utilized for a short period of time until the DUA spontaneously resolves or another form of treatment is instituted.

## CONCLUSIONS

There are many potential future treatments for DUA. Drug treatments require a more granular understanding of bladder, urethral and pelvic floor neurophysiology. A better understanding of how all the layers (urothelium, lamina propria, and muscularis propria) integrate with each other to provide efficient bladder emptying is needed. While stem cells and regenerative techniques appear to be the wave of the future, there need to be long-term studies to ensure that neoplasms do not form. Furthermore, increasing bladder contractions does not necessarily mean that the bladder outlet synchronously relaxes. Gene therapy can be contemplated, though this approach appears less favorable than stem cell and regenerative therapies. Neuromodulation techniques have advanced along with technology to involve studies using closed-loop feedback systems. Noninvasive transcranial stimulation approaches, used in many functional disorders, should be studied in DUA. While an indwelling motorized urethral device can assist with bladder emptying without use of a catheter, this device should be used for short time periods due to risks of foreign body in lower urinary tract. The future of treating DUA could involve a combination approach of all of the therapies discussed.

## CONFLICTS OF INTEREST

The authors have nothing to disclose.

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