HHS Public Access

Author manuscript

Curr Bladder Dysfunct Rep. Author manuscript; available in PMC 2016 December 01.

Published in final edited form as:

Curr Bladder Dysfunct Rep. 2015 December 1; 10(4): 325–331. doi:10.1007/s11884-015-0331-6.

Neurogenic Causes of Detrusor Underactivity

Brian T. Kadow, M.D., **Pradeep Tyagi, Ph.D.**, and **Christopher J. Chermansky, M.D.**

Department of Urology, University of Pittsburgh Medical Center, Pittsburgh, PA, U.S

Abstract

Detrusor underactivity (DU) is a poorly understood dysfunction of the lower urinary tract which arises from multiple etiologies. Symptoms of DU are non-specific, and a pressure-flow urodynamic study is necessary to differentiate DU from other conditions such as overactive bladder (OAB) or bladder outlet obstruction (BOO). The prevalence of DU ranges from 10–48%, and DU is most prevalent in elderly males. The pathophysiology underlying DU can be from both neurogenic and non-neurogenic causes. In this article, we review the neurogenic causes of detrusor underactivity, including diabetic bladder dysfunction, spinal cord injury, multiple sclerosis, Parkinson's disease, cerebrovascular accident, traumatic brain injury, and Fowler's syndrome. As knowledge about the underlying causes of DU advances, there have been several potential therapeutic approaches proposed to help those who suffer from this condition.

Keywords

Detrusor Underactivity; Underactive Bladder; Neurogenic Bladder; Urinary Retention

Introduction

Detrusor underactivity (DU) is a poorly understood dysfunction which arises due to multifactorial etiologies. The International Continence Society (ICS) defines DU as a bladder contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or failure to achieve complete bladder emptying within a normal time span[1]. As such, DU can only be diagnosed with pressure-flow urodynamic studies. Furthermore, there is no agreed-upon consensus of what defines reduced contraction strength, prolonged bladder emptying, or normal voiding time span. In contrast, an international expert group recently defined underactive bladder (UAB) as a symptom complex suggestive of DU, and UAB is usually characterized by prolonged urination time with or without a sensation of incomplete bladder emptying, usually with hesitancy, reduced sensation on filling, and slow

Corresponding Author: Christopher J Chermansky, M.D., University of Pittsburgh Medical Center, 300 Halket St, Suite 4710, Pittsburgh, PA 15213, Tel: (412)-641-8385 | Fax: (412)-641-3638, chermanskycj2@upmc.edu.

Conflict of Interest

B.T. Kadow: none; P. Tyagi: none; C.J. Chermansky: Although I am Co-investigator on 2 grants and a site PI on a multi-center industry trial, none is directly related to the material presented in this paper.

Compliance with Ethics Guideline

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

stream[2]. The UAB definition is difficult because it includes a complex array of symptoms that vary from patient to patient.

The prevalence of DU has been shown to increase with age, and studies suggest that it is more common in men. Jeong *et al.* studied the prevalence of DU among elderly men and women with non-neurogenic lower urinary tract symptoms undergoing urodynamic testing[3]. They diagnosed DU in 40% of men and 13% of women. Half of the men with DU and three quarters of the women with DU had other abnormalities such as detrusor overactivity (DO) and reduced bladder compliance. Another recent study of 181 community-dwelling elderly patients identified an age dependent increase in the prevalence of DU, with 48% of men and 12% of the women having impaired detrusor contractility (IDC) [4]. Concomitant bladder outlet obstruction (BOO) was seen in 40% of the men in this study, although BOO was seen in only 10% of the men with IDC. Both studies imply etiologies other than BOO are at play in the development of DU in elderly patients.

There are multiple etiologies of DU. The most well recognized mechanisms include myogenic dysfunction from fibrosis and the disruption of efferent neural pathways from traumatic neurologic injury or disease[5]. More recently, bladder and urethral afferent damage has been proposed in the development of DU[6]. Such altered afferent function can cause micturition to end early, resulting in a significant reduction of voiding efficiency. Thus, there are both neurogenic and non-neurogenic etiologies that lead to the development of DU. This article will review the neurogenic causes of DU, with a focus on recent research that highlights the underlying pathophysiology and will discuss potential therapeutic targets to treat this bothersome condition.

Diagnosis

The diagnosis of DU begins with a thorough discussion of a patient's medical history, noting any concomitant neurological diagnoses, diabetes mellitus (DM), or prior lower urinary tract or pelvic surgical procedures. A voiding diary can be helpful in clarifying the frequency and severity of a patient's symptoms. A careful physical and neurological examination should also be performed, and this exam should include evaluation of sacral dermatomes, perianal sensation, sphincter tone, and the presence or absence of a bulbocavernosus reflex[7]. Uroflowmetry in DU patients who still void often shows a decreased peak flow rate, prolonged voiding time, and elevated post-void residual; however, these findings are not specific since they may be seen in BOO[8].

Pressure-flow urodynamic testing is necessary to help differentiate DU from other conditions such as OAB or BOO. While there are currently no universally accepted urodynamic criteria to define DU, several parameters have been suggested to be diagnostic. These include a bladder contractility index (BCI) of <100 (PdetQmax + 5Qmax), detrusor pressure at max flow (PdetQmax) of <30mmH_2O and a maximum flow rate (Qmax) of <12ml/sec, and a bladder outlet obstruction index (BOOI) (PdetQmax – 2Qmax) of <20 and a Qmax of <12ml/sec[9–11]. Other groups have used Watts's factor to calculate detrusor contractility[12]. The common theme seen in all of these DU urodynamic criteria is that there

is an insufficient bladder contraction which results in prolonged and incomplete emptying in the absence of BOO.

Epidemiology

Several studies have evaluated the prevalence of DU in patients undergoing pressure-flow studies, and reported rates ranged from 10% to 48%; however, the patient populations and the urodynamic criteria to diagnose DU varied significantly amongst these studies[3, 4]. There was a trend towards an increase in the diagnosis of DU in older populations (particularly >75 years of age), and DU appears to be more common in men[13]. The true prevalence of DU is difficult to ascertain because of the varying urodynamic parameters used to define DU. Furthermore, the overall prevalence of DU is probably underestimated because there are likely a subset of patients with DU who are asymptomatic and do not present for urologic evaluation[13].

Current Treatment

Unfortunately, the current treatment of DU is rather limited. Behavioral modifications such as timed voiding or double voiding can help to reduce urinary stasis and its resultant sequelae, including frequency/urgency, cystitis, pyelonephritis, and bladder calculi. Also, some patients may have concomitant BOO, in which case alpha-adrenergic antagonists, 5-alpha reductase inhibitors, or transurethral resection of the prostate (TURP) can be employed to improve bladder emptying[14]. A recent study showed that men with mild or moderate DU and concomitant BPH who underwent photovaporization of the prostate showed significantly improved detrusor contractility (Pdet) and max flow rates (Qmax) compared to men with severe DU[15].

Some have advocated for the use of muscarinic agonists, such as bethanechol chloride, to increase detrusor contractility; however, countless studies have shown very limited efficacy with these medications[14, 16]. Unfortunately, many patients have persistent DU despite the previously mentioned treatments. Consequently, bladder drainage with either clean intermittent catheterization (CIC) or an indwelling catheter becomes necessary to achieve adequate bladder emptying and provide symptomatic relief. Catheterization regimens have been shown to adversely affect the quality of life in many patient populations[17].

Neurogenic Causes of Detrusor Underactivity

Diabetic Cystopathy

Given the increasing prevalence of DM, there has been a significant increase in the number of patients with diabetes-related urinary complications. It is known that up to 50% of men and women with DM will develop diabetic cystopathy, also known as diabetic bladder dysfunction[18, 19]. The types of diabetic bladder dysfunction range widely from sensory-urgency to impaired bladder emptying with eventual DU[18]. The onset of diabetic cystopathy can be insidious, occurring sometimes early after the onset of DM[20].

The pathophysiology of diabetic cystopathy is thought to be multifactorial and includes neuronal dysfunction, alterations in detrusor muscle physiology, and urothelial

dysfunction[21]. It is known that chronic hyperglycemia can lead to axonal nerve degradation from increased free radical formation, activation of the polyol pathway, protein kinase C activation, and increased formation of advanced glycated end products[22]. This neuronal damage is manifested as peripheral neuropathy, with diminished lower extremity sensation, gait instability, and/or neuralgia. Damage to bladder afferents can result in diminished bladder fullness because the stretch receptors within the bladder develop impaired signaling to the central nervous system (CNS).

Decreased levels of nerve growth factor (NGF) have been implicated as a cause of the neuronal dysfunction seen in diabetic cystopathy. NGF is a signaling protein that is critical in neuronal growth, maintenance, and survival[23]. In animal models of diabetic cystopathy, both NGF and NGF prophin-3 were found to be decreased by as much as 50% compared to non-diabetic controls[24]. Furthermore, the same authors injected a replication-defective Herpes Simplex Vector (HSV)-1 vector carrying the β-NGF gene into the bladders of diabetic rats to restore decreased NGF expression in both the bladder and the bladder afferent pathways[24]. The increase in NGF expression improved voiding function, as evidenced by a reduction in bladder capacity and a decrease in post void residuals compared to control animals. This further elucidates the role of NGF in diabetic cystopathy.

Spinal Cord Injury

Bladder dysfunction after SCI is a leading cause of morbidity and hospitalizations in this patient population, and UTIs are responsible for 20% of all hospitalizations in the first year of diagnosis[25]. Most patients with SCI will initially develop DU or detrusor areflexia during spinal shock before they exhibit chronic bladder dysfunction.

The type of bladder dysfunction that develops after spinal shock is dependent on the level of the cord lesion. For patients with suprasacral SCI, the parasympathetic nerves and spinal sensory centers within the sacral cord are preserved; however the communication between the sacral cord and the pontine micturition center (PMC) is impaired[26]. After the acute phase of spinal shock, there is synaptic reorganization between the sacral cord and the bladder which often leads to involuntary reflex bladder contractions, termed neurogenic detrusor overactivity (NDO). Voluntary inhibition of the micturition reflex is lost. The PMC is critical in coordinating external urethral relaxation prior to detrusor contraction. Detrusor-external sphincter dyssynergia (DESD) is characterized by involuntary contractions of the external urethral sphincter during an involuntary detrusor contraction. DESD leads to high detrusor storage pressures and incomplete bladder emptying. Over time, untreated DESD can lead to detrusor underactivity with resultant cystitis, bladder wall thickening, bladder calculi, and upper tract deterioration. Prior to the introduction of CIC and muscarinic antagonists, neurogenic bladder from SCI was a leading cause of morbidity and hospitalizations[27].

For patients with sacral SCI, the sacral parasympathetic nucleus, which controls bladder emptying and Onuf's nucleus, which excites the external urethral sphincter, can both be damaged. This results in detrusor areflexia with high or normal compliance and a loss of normal bladder sensation. Because of initial low intravesical pressures, sacral SCI patients have a low risk of upper tract deterioration compared to suprasacral SCI patients; however,

sacral SCI patients can develop decreased compliance from neurologic decentralization[26]. As such, these patients must be monitored with urodynamic testing on a regular basis.

An interesting area of recent research in SCI-related bladder dysfunction is the synaptic reorganization that occurs following SCI. Several studies have shown that neurotrophins are important mediators of post-SCI synaptic reorganization[28, 29]. One well-studied neurotrophin is NGF, and it has been shown that elevated NGF levels correlate with the likelihood of DESD in the SCI population[30]. Further research is necessary to characterize NGF levels in DU. Another neurotrophin that has been suggested to be important in synaptic reorganization after SCI is brain-derived neurotrophic factor (BDNF), which is abundant in the CNS and modulates neuroplasticity at the spinal cord level[31]. Frias and colleagues showed that BDNF sequestration inhibited the development of NDO and improved bladder function in chronic-SCI rats[32].

Because DU after SCI is the result of damaged circuitry that regulates detrusor contractility and bladder sensation, there has been interest in artificially modulating the nervous system to both contract the detrusor and relax the external urethral sphincter[33]. An implantable device was created in the late 1970's by Brindley to stimulate the anterior sacral nerve roots S2–S4. Electrical stimulation at low frequencies (10–30Hz) was noted to induce detrusor contraction with concurrent external sphincteric contraction[34]. Furthermore, with intermittent stimulation, there was both sphincteric relaxation and detrusor contraction, thereby allowing bladder emptying at low detrusor pressures. Several stimulation/relaxation cycles were typically necessary to achieve adequate emptying[35]. While this device has shown promise, it has not been widely adopted as a treatment for DU in SCI patients. More recently, Sievert et al investigated the benefit of early implantation of sacral nerve modulators during the acute phase of DU following thoracic SCI. and found that early implantation of these devices mitigated the development of NDO and improved urinary continence rates[36].

Multiple Sclerosis

Multiple sclerosis (MS) is an acquired, autoimmune-mediated demyelinating disorder of the CNS. MS is most commonly diagnosed between ages 20–50 years of age, and it has a 2:1 female to male prevalence[37]. The common pathologic finding in MS is focal demyelination and plaque formation throughout the brain and spinal cord, and this pathology can result in a delayed or complete nerve conduction block[38]. There is a high prevalence of bladder dysfunction in the MS population, with up to 90% experiencing lower urinary tract symptoms (LUTS) and/or urinary incontinence[38]. Approximately 10% of patients with MS are initially diagnosed when they present for urologic evaluation, and it is important for clinicians to keep this diagnosis in mind when evaluating patients with LUTS and concomitant neurologic symptoms.

The bladder symptoms that are most prevalent in patients with MS include frequency, urgency, UUI, and urinary retention. Urodynamic evaluation is essential in the evaluation of these patients, and the typical urodynamic findings include neurogenic DO in over 60% of patients and DU in 20% of patients[40, 41]. DESD is another common and concerning urodynamic finding in patients with MS. As with many of the other causes of neurogenic

DU, the location of the neurologic lesion plays a critical role in the type of resultant bladder dysfunction. Studies have shown that patients with cervical cord lesions or pontine lesions are more likely to suffer from emptying symptoms, including DU, whereas those with cerebral cortex lesions are more prone to storage symptoms such as DO[42].

Cerebrovascular Accident

Bladder symptoms are often reported following cerebrovascular accident (CVA). In the acute phase after CVA, there is a high rate of urinary retention and many patients require either an indwelling urethral catheter or CIC for a period of time. Burney *et al*. performed urodynamic evaluations on 60 patients within 72 hours following a CVA and found that nearly 50% of patients had urinary retention, mainly due to detrusor areflexia[43]. Furthermore, they noted that urinary retention from detrusor areflexia was more common in patients who had a hemorrhagic infarct (85%) as compared to patients with ischemic infarcts (10%). Also, a recent study evaluating patients with urinary retention during the acute phase of stroke found that 54.5% of patients had detrusor areflexia on urodynamic evaluation[44]. Patients with aphasia, diabetes mellitus, and a lower functional status had higher rates of urinary retention, and these patients were more likely to require an indwelling catheter or CIC. Additionally, although urinary retention related to detrusor areflexia is very common in the acute phase following CVA, over 95% of these patients will see resolution of their urinary retention within 2 months[45].

Multiple studies have correlated the location of the CVA lesion with either bladder storage or emptying dysfunction[43, 45]. Yum *et al.* evaluated 30 patients with brainstem infarcts and divided patients into those with either pontine or medullary infarcts[46]. Reduced bladder capacity was seen more often in patients with pontine infarcts (62%) compared to patients with medullary infarcts (11%). Conversely, DU was more common in patients with medullary infarcts (55%) compared to those with pontine infarcts (10%). In addition, Cho *et al.* showed that patients with lateral medullary infarcts have higher rates of DU because of damage to the descending pathways from the PMC[47]. Yet, other studies have suggested that the location of the infarct does not correlate with the resultant type of voiding dysfunction[42]. An important point to consider in evaluating CVA patients is that they often have other co-morbidities, such as DM or prior neurologic diseases, and this history can contribute to their bladder dysfunction.

Traumatic Brain Injury

Bladder dysfunction, including DU, is often found in traumatic brain injury (TBI) patients. Retrospective studies of TBI patients undergoing urodynamics suggest that bladder dysfunction is present in 30–85% of TBI patients[48–50]. The underlying pathophysiology of TBI bladder dysfunction is often multifactorial, including damage to the brain areas that coordinate normal micturition, communication deficits, and cognitive impairment. The location and extent of the brain injury also correlates with the type and severity of bladder dysfunction[48]. Giannantoni *et al.* studied voiding dysfunction amongst 57 coma survivors after TBI, and they found that 85% of these patients had bladder dysfunction[51]. Pressure-flow urodynamics showed DU in 32% of these patients, and 83% of the DU patients had prolonged voiding times, urine intermittency, and pseudodyssynergia.

Moody and colleagues used a rat model to evaluate the link between TBI and voiding dysfunction[52]. Ten rats underwent urodynamics before and after undergoing a lateral fluid percussion-induced brain injury. The micturition reflex was altered in these animals, with incomplete bladder emptying and continuous urinary incontinence. This was transient in 83% of the rats and permanent in the other 17%. The authors hypothesized that TBI induces neural dysregulation that changes the conditions for afferent signal translation and transmission, though the exact mechanisms underlying these changes remain unknown.

Parkinson's Disease

Parkinson's disease (PD) is a movement disorder that is associated with the degradation of dopaminergic neurons in the substantia nigra of the basal ganglia. PD results in symptoms such as tremors, rigidity, bradykinesia, and postural instability. These patients also have autonomic nervous disorders, and bladder dysfunction commonly results. The brain areas affected by PD that cause voiding dysfunction include the frontal cortex, basal ganglia, thalamus, anterior cingulate gyrus, and the caudate nucleus[53]. The most common bladder dysfunction found in PD patients is NDO[54]. The etiology of NDO is thought to be related to a dysregulation of the PMC in the basal ganglia that affects the voluntary control of the micturition reflex[55].

DU is also seen in PD. In one series DU was noted in 16% of PD patients[56]. In contrast, Liu *et al.* performed urodynamics in 58 PD patients and found DU in 53% of those tested[57]. The pathophysiology underlying DU in PD is currently not well understood, although studies have correlated DU to the patient's overall motor function[57]. Both pseudodyssynergia of the EUS during NDO and bradykinesia of the EUS during the onset of voluntary micturition can occur in PD patients[58]. Both of these EUS abnormalities can lead to impaired detrusor contractility and DU. Finally, men with both PD and BOO from BPH are often initially managed without definitive surgery to resolve the BOO in a timely manner because of concern for UI post-surgery[59]. This can lead to bladder decompensation and eventual DU. Yet, Roth reported a 70% success rate after TURP in 23 PD patients with no cases of de novo urinary incontinence[60].

Fowler's Syndrome

Fowler's syndrome was first described in 1985 in young women with urinary retention[61]. The sphincter EMG signal in these women contains repetitive discharges and decelerating bursts. This impairs sphincter relaxation and leads to obstructed voiding and either incomplete or complete urinary retention. The development of the sphincteric abnormality may be under the influence of estrogens, as suggested by the high association of polycystic ovaries in these women[62]. Sacral neuromodulation has a rapid effect in restoring voiding function in these women, suggesting that it works by reversing the inhibitory effect of the sphincter contraction[41]. In 1999 the FDA approved sacral neuromodulation for non-obstructive urinary retention, and sacral neuromodulation can be used as a treatment for DU in patients with Fowler's syndrome.

Future Therapeutic Directions

As previously mentioned, the current treatment of DU is rather limited to either CIC or an indwelling catheter. To date, therapies such as cholinergic agents have been used unsuccessfully to treat DU[63]. As this disease is becoming better studied, several potential therapeutic targets have been identified that may ultimately be beneficial in the treatment of DU patients. Acetylcholinesterase inhibitors are a potential option to treat DU by extending the duration of action for acetylcholine. Distigmine bromide, an acetylcholinesterase inhibitor, was recently tested on 27 DU patients[64]. At a dose of 5mg given three times daily for 4 weeks, distigmine bromide significantly reduced PVR and eliminated the need for CIC in 11 patients. Additionally, the action of acetylcholine can be increased by activating presynaptic muscarinic M1 receptors found within bladder efferent nerves. Cevimeline, an M1 agonist approved for xerostomia, was studied in rats and guinea pigs[65]. At doses of 0.3 mg/kg or higher, cevimeline increased non-voiding and phasic contractions. Preclinical evidence for cevimeline justifies clinical testing in DU patients.

Other FDA approved drugs that could potentially treat DU include ampyra and fampridine[66]. These drugs potentiate the release of neurotransmitters from both sensory and motor nerve terminals, thereby potentially improving detrusor contractility[67]. The intravenous administration of Ampyra improved bladder emptying in urethane-anesthetized rats[68]. In addition, cannabinoid-1 receptors (CB1) antagonists such as rimonabant, used in the treatment of obesity, can be potential DU drugs[69]. Animal studies demonstrated that CB1 antagonists increased afferent input from bladder and reduced the bladder capacity[70]. Another potential category is TRPV4 agonists, which increases afferent signaling without evoking pain. It is thought that TRPV4 stimulation facilitates the micturition reflex by activating mechanosensitive, capsaicin insensitive C-fibers. GSK 1016790A, a TRPV4 agonist, transiently decreased bladder capacity and increased voided volumes after intravesical instillation in Sprague-Dawley rats[71].

The use of stem cells is another potential therapy for DU that is under investigation. Levanovich recently reported on a 79 year old male with DU that had previously undergone 2 TURPs, failed bethanechol chloride, and was dependent on CIC 4–6 times/day for many years[72]. The patient underwent a quadriceps muscle biopsy, and muscle-derived stem cells were isolated and injected into his detrusor. The Global Response Assessment questionnaire was used, and the patient was noted to have “moderate improvement” of his DU symptoms at 6 and 12 months post-injection. Repeat urodynamic s at 3 months post-injection showed that the sensation of first desire to void decreased from 711 cc to 365 cc. He was also able to void small volumes of urine at 3 months post-injection, but he has remained dependent on CIC at 1 year post-injection. Although this publication was a case report of one patient, it presents an exciting potential for the use stem cells to treat DU.

Conclusion

Detrusor underactivity remains a poorly treated bladder dysfunction, and many patients remain frustrated with the morbidity of recurrent UTIs and intermittent hematuria that result from either CIC or an indwelling catheter. Patients with neurologic disease who lack the

dexterity needed to do CIC find these complications even more frustrating. There are multiple etiologies of DU, and in this article we have highlighted the most common neurogenic causes of the condition. Furthermore, we highlighted current research directions into the treatment of DU as it pertains to patients with neurogenic diagnoses. As advances are made into understanding better the pathophysiology of DU, several more therapeutic targets may be identified to better treat these afflicted patients.

Acknowledgments

Funding:

Support provided in part from NIH/NIDDK grant DK093424

References

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

1. Abrams P, Cardozo L, Fall M, et al. The Standardisation of Terminology of Lower Urinary Tract Function: Report from the Standardisation Sub-Committee of the International Continence Society. Neurourol Urodyn. 2002; 21:167–178. [PubMed: 11857671]
2. Chapple CR, Osman NI, Birder L, et al. The Underactive Bladder: A New Clinical Concept? Eur Urol. 2015; 68:351–353. [PubMed: 25770481]
3. Jeong SJ, Kim HJ, Lee YJ, et al. Prevalence and Clinical Features of Detrusor Underactivity among Elderly with Lower Urinary Tract Symptoms: A Comparison between Men and Women. Korean Journal of Urology. 2012; 53:342–348. [PubMed: 22670194]
4. Abarbane J, Marcus EL. Impaired Detrusor Contractility in Community-Dwelling Elderly Presenting with Lower Urinary Tract Symptoms. Urology. 2007; 69:436–440. [PubMed: 17382138]
5. Osman NI, Chapple CR. Contemporary Concepts in the Aetiopathogenesis of Detrusor Underactivity. Nat Rev Urol. 2014; 11:639–648. [PubMed: 25330789]
6. Smith PP. Aging and the Underactive Detrusor: A Failure of Activity or Activation? Neurourol Urodyn. 2010; 29:408–412. [PubMed: 19760756]
7. Miyazato M, Yoshimura N, Chancellor MB. The Other Bladder Syndrome: Underactive Bladder. Rev Urol. 2013; 15:11–22. [PubMed: 23671401]
8. Frimodt-Moller C. Diabetic Cystopathy. A Review of the Urodynamic and Clinical Features of Neurogenic Bladder Dysfunction in Diabetes Mellitus. Dan Med Bull. 1978; 25:49–60. [PubMed: 344005]
9. Abrams P. Bladder Outlet Obstruction Index, Bladder Contractility Index and Bladder Voiding Efficiency: Three Simple Indices to Define Bladder Voiding Function. BJU Int. 1999; 84:14–15. [PubMed: 10444116]
10. Lim C, Abrams P. The Abrams-Griffiths Nomogram. World J Urol. 1995; 13:34–39. [PubMed: 7539679]
11. Schafer W. Analysis of Bladder-Outlet Function with the Linearized Passive Urethral Resistance Relation, LinPURR, and a Disease-Specific Approach to Grading Obstruction: From Complex to Simple. World J Urol. 1995; 13:47–58. [PubMed: 7773317]
12. Oelke M, Rademakers KL, van Koeveringe GA, et al. Unraveling Detrusor Underactivity: Development of a Bladder-Outlet Resistance - Bladder Contractility Nomogram for Adult Male Patients with Lower Urinary Tract Symptoms. Neurol Urodyn. 2015 Epub ahead of print.
13••. Drake MJ, Williams J, Bijos DA. Voiding Dysfunction Due to Detrusor Underactivity: An Overview. Nat Rev Urol. 2014; 11:454–464. This article is an excellent overview of the multiple

etiologies of DU, the current limitations in treatment, and potential therapeutic targets that have recently been identified to help patients with this condition. [PubMed: 25002201]

14. Chancellor MB, Kaufman J. Case for Pharmacotherapy Development for Underactive Bladder. Urology. 2008; 72:966–967. [PubMed: 18774593]
15. Yu Z, Li J, Li Z, et al. Photoselective Vaporization of the Prostate and Simultaneous Suprapubic Cystostomy for the Treatment of Benign Prostatic Hyperplasia in Patients with Mild to Severe Detrusor Underactivity. Urol Int. 2015 Epub ahead of print.
16. Krishnamoorthy S, Kekre NS. Detrusor Underactivity: To Tone or Not to Tone the Bladder? Indian Journal of Urology. 2009; 25:407–408. [PubMed: 19881143]
17. Liu CW, Attar KH, Gall A, et al. The Relationship between Bladder Management and Health-Related Quality of Life in Patients with Spinal Cord Injury in the UK. Spinal Cord. 2010; 48:319–324. [PubMed: 19841636]
18. Arrellano-Valdez F, Urrutia-Osorio M, Arroyo C, et al. A Comprehensive Review of Urologic Complications in Patients with Diabetes. Springerplus. 2014; 3:549. [PubMed: 25332855]
19. Nirmal J, Tyagi P, Chuang YC, et al. Functional and Molecular Characterization of Hyposensitive Underactive Bladder Tissue and Urine in Streptozotocin-Induced Diabetic Rat. PLoS One. 2014; 9:e102644. [PubMed: 25050870]
20. Sasaki K, Yoshimura N, Chancellor MB. Implications of Diabetes Mellitus in Urology. Urol Clin North Am. 2003; 30:1–12. [PubMed: 12580554]
21. Yoshimura N, Chancellor MB, Andersson KE, et al. Recent Advances in Understanding the Biology of Diabetes-Associated Bladder Complications and Novel Therapy. BJU Int. 2005; 95:733–738. [PubMed: 15794773]
22. Fedele D. Therapy Insight: Sexual and Bladder Dysfunction Associated with Diabetes Mellitus. Nat Clin Pract Urol. 2005; 2:282–290. [PubMed: 16474810]
23. Levi-Montalcini R. The Nerve Growth Factor 35 Years Later. Science. 1987; 237:1154–62. [PubMed: 3306916]
24. Sasaki K, Chancellor MB, Goins WF, et al. Gene Therapy Using Replication-Defective Herpes Simplex Virus Vectors Expressing Nerve Growth Factor in a Rat Model of Diabetic Cystopathy. Diabetes. 2004; 53:2723–2730. [PubMed: 15448108]
25. Manack A, Motsko SP, Haag-Molkenteller C, et al. Epidemiology and Healthcare Utilization of Neurogenic Bladder Patients in a US Claims Database. Neurourol Urodyn. 2011; 30:395–401. [PubMed: 20882676]
26. Cruz CD, Coelho A, Antunes-Lopes T, et al. Biomarkers of Spinal Cord Injury and Ensuing Bladder Dysfunction. Adv Drug Deliv Rev. 2015; 82–83:153–159.
27. Lapides J, Diokno AC, Silber SJ, et al. Clean Intermittent Self-Catheterization in the Treatment of Urinary Tract Disease. Journal of Urology. 1972; 107:458–461. [PubMed: 5010715]
28. Pezet S, McMahon SB. Neurotrophins: Mediators and Modulators of Pain. Annu Rev Neurosci. 2006; 29:507–538. [PubMed: 16776595]
29. Vizzard MA. Neurochemical Plasticity and the Role of Neurotrophic Factors in Bladder Reflex Pathways after Spinal Cord Injury. Prog Brain Res. 2006; 152:97–115. [PubMed: 16198696]
30. Kuo HC, Liu HT, Chancellor MB. Can Urinary Nerve Growth Factor Be a Biomarker for Overactive Bladder? Reviews in Urology. 2010; 12:e69–e77. [PubMed: 20811555]
31. Song QX, Chermansky CJ, Birder LA, et al. Brain-Derived Neurotrophic Factor in Urinary Continence and Incontinence. Nat Rev Urol. 2014; 11:579–588. [PubMed: 25224451]
32. Frias B, Santos J, Morgado M, et al. The Role of Brain-Derived Neurotrophic Factor (Bdnf) in the Development of Neurogenic Detrusor Overactivity (NDO). J Neurosci. 2015; 35:2146–2160. [PubMed: 25653370]
33. Ren J, Chew DJ, Biers S, et al. Electrical Nerve Stimulation to Promote Micturition in Spinal Cord Injury Patients: A Review of Current Attempts. Neurourol Urodyn. 2015 Epub ahead of print.
34. Brindley GS. An Implant to Empty the Bladder or Close the Urethra. J Neurol Neurosurg Psychiatry. 1977; 40:358–369. [PubMed: 406364]
35. Brindley GS, Polkey CE, Rushton DN. Sacral Anterior Root Stimulators for Bladder Control in Paraplegia. Paraplegia. 1982; 20:365–381. [PubMed: 6984503]

36. Sievert KD, Amend B, Gakis G, et al. Early Sacral Neuromodulation Prevents Urinary Incontinence after Complete Spinal Cord Injury. Ann Neurol. 2010; 67:74–84. [PubMed: 20186953]
37. Corcos J. A Urological Challenge: Voiding Dysfunction in Multiple Sclerosis. Can Urol Assoc J. 2013; 7:S181–S182. [PubMed: 24523839]
38. Hinson JL, Boone TB. Urodynamics and Multiple Sclerosis. Urol Clin North Am. 1996; 23:475–481. [PubMed: 8701560]
39. Leboeuf, L.; Cohen, B.; Gousse, AE. Multiple Sclerosis. In: Corcos, J.; Schick, E., editors. Textbook of the Neurogenic Bladder. CRC Press; 2008.
40. Litwiller SE, Frohman EM, Zimmern PE. Multiple Sclerosis and the Urologist. J Urol. 1999; 161:743–757. [PubMed: 10022678]
41. DasGupta R, Fowler CJ. Bladder, Bowel and Sexual Dysfunction in Multiple Sclerosis: Management Strategies. Drugs. 2003; 63:153–166. [PubMed: 12515563]
42. Araki I, Matsui M, Ozawa K, et al. Relationship of Bladder Dysfunction to Lesion Site in Multiple Sclerosis. J Urol. 2003; 169:1384–1387. [PubMed: 12629367]
43. Burney TL, Senapati M, Desai S, et al. Acute Cerebrovascular Accident and Lower Urinary Tract Dysfunction: A Prospective Correlation of the Site of Brain Injury with Urodynamic Findings. J Urol. 1996; 156:1748–1750. [PubMed: 8863586]
44. Kim TG, Chun MH, Chang MC, et al. Outcomes of Drug-Resistant Urinary Retention in Patients in the Early Stage of Stroke. Ann Rehabil Med. 2015; 39:262–267. [PubMed: 25932423]
45. Kong KH, Young S. Incidence and Outcome of Post-Stroke Urinary Retention: A Prospective Study. Arch Phys Med Rehabil. 2000; 81:1464–1467. [PubMed: 11083349]
46. Yum KS, Na SJ, Lee KY, et al. Pattern of Voiding Dysfunction after Acute Brainstem Infarction. Eur Neurol. 2013; 70:291–296. [PubMed: 24052006]
47. Cho HJ, Kang TH, Chang JH, et al. Neuroanatomical Correlation of Urinary Retention in Lateral Medullary Infarction. Ann Neurol. 2015; 77:726–733. [PubMed: 25627980]
48. Ersoz M, Tunc H, Akyuz M, et al. Bladder Storage and Emptying Disorder Frequencies in Hemorrhagic and Ischemic Stroke Patients with Bladder Dysfunction. Cerebrovasc Dis. 2005; 20:395–399. [PubMed: 16205058]
49. Kulakli F, Koklu K, Ersoz M, et al. Relationship between Urinary Dysfunction and Clinical Factors in Patients with Traumatic Brain Injury. Brain Inj. 2014; 28:323–327. [PubMed: 24377376]
50. Chua K, Chuo A, Kong KH. Urinary Incontinence after Traumatic Brain Injury: Incidence, Outcomes and Correlates. Brain Inj. 2003; 17:469–478. [PubMed: 12745703]
51. Giannantoni A, Silvestro D, Siracusano S, et al. Urologic Dysfunction and Neurologic Outcome in Coma Survivors after Severe Traumatic Brain Injury in the Postacute and Chronic Phase. Arch Phys Med Rehabil. 2011; 92:1134–1138. [PubMed: 21704794]
52. Moody BJ, Liberman C, Zvara P, et al. Acute Lower Urinary Tract Dysfunction (LUTD) Following Traumatic Brain Injury (Tbi) in Rats. Neurourol Urodyn. 2014; 33:1159–1164. [PubMed: 24038177]
53. Badr AV, Purohit RS, Skenazy J, et al. A Review of Lower Urinary Tract Symptoms in Patients with Parkinson's disease. Curr Urol Rep. 2014; 15:435. [PubMed: 25002072]
54. Ransmayr GN, Holliger S, Schletterer, et al. Lower Urinary Tract Symptoms in Dementia with Lewy Bodies, Parkinson Disease, and Alzheimer Disease. Neurology. 2008; 70:299–303. [PubMed: 18209204]
55. Blackett H, Walker R, Wood B. Urinary Dysfunction in Parkinson's disease: A Review. Parkinsonism Relat Disord. 2009; 15:81–87. [PubMed: 18474447]
56. Araki IM, Kitahara M, Oida T, et al. Voiding Dysfunction and Parkinson's disease: Urodynamic Abnormalities and Urinary Symptoms. J Urol. 2000; 164:1640–16433. [PubMed: 11025724]
57. Liu Z, Uchiyama T, Sakakibara R, et al. Underactive and Overactive Bladders Are Related to Motor Function and Quality of Life in Parkinson's disease. Int Urol Nephrol. 2015; 47:751–757. [PubMed: 25792006]

58. Campeau L, Soler R, Andersson KE. Bladder Dysfunction and Parkinsonism: Current Pathophysiological Understanding and Management Strategies. Curr Urol Rep. 2011; 12:396–403. [PubMed: 21986769]

59. Staskin DS, Vardi Y, Siroky MB. Post-Prostatectomy Continence in the Parkinsonian Patient: The Significance of Poor Voluntary Sphincter Control. J Urol. 1988; 140:117–118. [PubMed: 2454326]

60. Roth B, Studer UE, Fowler CJ, et al. Benign Prostatic Obstruction and Parkinson's Disease--Should Transurethral Resection of the Prostate Be Avoided? J Urol. 2009; 181:2209–2213. [PubMed: 19296974]

61. Fowler CJ, Kirby RS. Abnormal Electromyographic Activity (Decelerating Burst and Complex Repetitive Discharges) in the Striated Muscle of the Urethral Sphincter in 5 Women with Persisting Urinary Retention. Br J Urol. 1985; 57:67–70. [PubMed: 4038618]

62. Fowler CJ, Christmas TJ, Chapple CR, et al. Abnormal Electromyographic Activity of the Urethral Sphincter, Voiding Dysfunction, and Polycystic Ovaries: A New Syndrome? 1988; 297:1436–1438.

63••. Smith PP, Tyagi P, Kuchel GA, et al. Advanced Therapeutic Directions to Treat the Underactive Bladder. Int Urol Nephrol. 2014; 46 (Suppl 1):S35–44. This article is an excellent review of the potential therapeutic targets to improve detrusor contractility in patients with DU. [PubMed: 25238893]

64. Bougas DA, Mitsogiannis IC, Mitropoulos DN, et al. Clinical Efficacy of Distigmine Bromide in the Treatment of Patients with Underactive Detrusor. Int Urol Nephrol. 2004; 36:507–512. [PubMed: 15787326]

65. Witsell DL, Stinnett S, Chambers MS. Effectiveness of Cevimeline to Improve Oral Health in Patients with Postradiation Xerostomia. Head Neck. 2012; 34:1136–1142. [PubMed: 22231734]

66. Cardenas DD, Ditunno JF, Graziani V, et al. Two Phase 3, Multicenter, Randomized, Placebo-Controlled Clinical Trials of Fampridine-SR for Treatment of Spasticity in Chronic Spinal Cord Injury. Spinal Cord. 2014; 52:70–76. [PubMed: 24216616]

67. Wu ZZ, Li DP, Chen SR, et al. Aminopyridines Potentiate Synaptic and Neuromuscular Transmission by Targeting the Voltage-Activated Calcium Channel Beta Subunit. J Biol Chem. 2009; 284:36453–36461. [PubMed: 19850918]

68. Maggi CA, Santicioli P, Borsini F, et al. The Effect of 4-Aminopyridine on Micturition Reflex in Normal or Capsaicin-Desensitized Rats. Brain Res. 1988; 449:61–70. [PubMed: 2840174]

69. Pataky Z, Gasteyger C, Ziegler O, et al. Efficacy of Rimonabant in Obese Patients with Binge Eating Disorder. Experimental and Clinical Endocrinology & Diabetes German Society of Endocrinology [and] German Diabetes Association. 2013; 121:20–26.

70. Dmitrieva N, Berkley KJ. Contrasting Effects of Win 55212-2 on Motility of the Rat Bladder and Uterus. J Neurosci. 2002; 22:7147–7153. [PubMed: 12177210]

71. Aizawa N, Wyndaele JJ, Homma Y, et al. Effects of TRPV4 Cation Channel Activation on the Primary Bladder Afferent Activities of the Rat. Neurourol Urodyn. 2012; 31:148–55. [PubMed: 22038643]

72•. Levanovich PE, Diokno A, Hasenau DL, et al. Intradetrusor Injection of Adult Muscle-Derived Cells for the Treatment of Underactive Bladder: Pilot Study. Int Urol Nephrol. 2015; 47:465–467. This case report of a single patient with DU who received intradetrusor injection of muscle-derived stem cells with resultant improvement in voiding function represents an exciting potential regenerative treatment for patients with DU. [PubMed: 25663053]