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REVIEW

OnabotulinumtoxinA in the treatment of neurogenic bladder

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Abstract: This review examines the evidence for use of onabotulinumtoxinA in the treatment of neurogenic lower urinary tract dysfunction. Since its first use in 1988 to treat detrusor sphincter dyssynergia, use of botulinum toxin has increased in this group of patients. We discuss the mechanism of action, patient selection, dosing, efficacy, and side effect profile of this now licensed treatment option.

Keywords: neurogenic bladder, botulinum toxin, onabotulinumtoxinA, neurogenic detrusor overactivity, detrusor sphincter dyssynergia

Introduction

The normal function of the lower urinary tract in storage and voiding of urine is coordinated by neural control within the brain and spinal cord. Consequently, any interruption to this system affecting bladder or outflow function may lead to symptoms of neurogenic bladder or neurogenic lower urinary tract dysfunction (NLUTD). Table 1 lists the various causes of NLUTD. Patients with NLUTD can be asymptomatic and may be at risk of long-term complications, the most significant of which is damage to renal function. This is secondary to high bladder storage pressures with or without vesicoureteric reflux.[1] Elevated bladder pressures may be due to detrusor overactivity or poor bladder compliance during storage, as well as detrusor muscle contractions against a closed sphincter known as detrusor sphincter dyssynergia. The nature and extent of symptoms is dependent on the type of pathology, severity, and location within the nervous system. Therefore, treatment and long-term management varies according to the underlying disease process and resulting symptoms.

The overall prevalence of NLUTD is unknown, but the relative risk of developing NLUTD in relation to specific pathologies is better understood. It often accompanies spinal cord injury, basal ganglia pathology, demyelinating disorders, and cerebrovascular pathology. The causes of spinal cord injury are multifactorial. They can be traumatic, vascular, congenital, or medical in origin. Patients with lesions above T10 with upper motor neuron type injury will suffer from NLUTD consisting of neurogenic detrusor overactivity and detrusor sphincter dyssynergia. Those with lesions below L2 and a lower motor neuron type injury will likely have an atonic bladder.[2] Historically, renal failure was the leading cause of death in patients with spinal cord injury.[3] More recently, an emphasis on identifying and managing at-risk patients has resulted in improvements in preservation of renal function and symptom control, with respiratory diseases now being the more common cause of mortality in patients with spinal cord injury.[4]

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Table 1 Causes of neurogenic lower urinary tract dysfunction

Spinal cord lesion	Spinal cord injury
	Congenital nerve tube defects
Basal ganglia pathology	Parkinson disease
	Huntington's disease
	Shy-Drager syndrome
Demyelinating disorders	Multiple sclerosis
Cerebrovascular pathology	Stroke
	Cerebral palsy
Iatrogenic	Spine and pelvic surgery

Basal ganglia pathology, including Parkinson's disease, Huntington's disease, and Shy-Drager syndrome are strongly associated with NLUTD. In patients with Parkinson's disease, NLUTD is apparent in 37.9%–70% of cases.[5] However, it is likely that an element of age-related lower urinary tract dysfunction plays a role, as is the case in patients with dementia.

Multiple sclerosis causes NLUTD in 50%–90% of patients. They are frequently asymptomatic and often those with lower urinary tract symptoms are not referred for urological assessment early on.[6] The rate of NLUTD in patients with brain tumors is 24%, and 30%–40% in cerebral palsy. Patients with peripheral neuropathy caused primarily by diabetes and/or alcohol abuse as well as those having had spinal or pelvic surgery are also at risk. It is important to recognize and diagnosis NLUTD early because irreversible changes within the lower urinary tract may occur.[7]

Diagnosis starts with a thorough history and focused neurological and urological examination. Overall mobility and hand function should also be assessed. Further assessment with urinalysis, urea and electrolytes, uroflowmetry, and measured residual volume coupled with a bladder diary forms a mandatory prelude to more invasive but also more objective evaluation of the lower urinary tract with urodynamic studies. Video urodynamics is the gold standard for urodynamic assessment of the lower urinary tract.[5] It encompasses evaluation of the storage phase (filling cystometry) with the voiding phase (pressure-flow studies). The key urodynamic features of the storage phase include detrusor overactivity, small bladder capacity, incontinence, ureteric reflux, and poor bladder compliance. Those of the voiding phase include reduced flow, reduced or absent detrusor function, and intermittent flow, which may be suggestive of detrusor sphincter dyssynergia and a post void residual volume.

There are several classification systems for NLUTD, but the European Association of Urology recommends a functional classification based on activity of the detrusor and external urinary sphincter.[8] Either can be overactive, normoactive, or underactive.

Current and emerging therapies

The treatment of NLUTD centers on protecting the upper urinary tract, managing urinary incontinence, and ultimately improving the patient's quality of life. In order to avoid renal injury, it is necessary to maintain intravesical pressure within safe limits during both the filling and voiding phase of bladder function.[9] Identifying exacerbating factors, modifying behavior patterns, reducing infections, biofeedback, and pelvic floor strengthening are the mainstay of conservative management. Current and emerging treatments for NLUTD are summarized in Table 2.

Pharmacologic treatment of NLUTD using antimuscarinic drugs is well established. Muscarinic receptor antagonists act by binding to post-synaptic muscarinic receptors, thereby stabilizing the detrusor muscle and reducing involuntary contractions. A recent systematic review found greater symptomatic improvement and significant reduction in intravesical pressures when compared with placebo.[10] Our systematic review did not find any studies reporting quality of life outcomes. It must also be noted that because muscarinic receptors are not confined to the urinary tract, side effects such as dry mouth and constipation limit their tolerability and long-term patient compliance with treatment. This is even moreso the case in patients with NLUTD because higher doses of antimuscarinic agents are required compared with a non-neurogenic population.[11]

Drugs may also be required to decrease the outlet resistance by relaxing the external urinary sphincter. However, these do not exist and so alpha antagonists may be used in selected cases to relax the bladder neck sphincter instead, which may improve bladder emptying.[12] In a small cohort of 10 men with spinal cord injury and upper tract stasis, use of alpha blockers has been shown to resolve upper tract stasis in men who used reflex voiding.[13]

Table 2 Summary of current and emerging therapeutic options for neurogenic lower urinary tract dysfunction

Current	Emerging
Noninvasive	
Antimuscarinics	Electrical and magnetic stimulation
Alpha blockers	
Invasive	
Intermittent self catheterization	Intravesical botulinum toxin
Cystoplasty	Sacral neuromodulation
Bladder autoaugmentation	
Urinary diversion	
Indwelling catheterization	

Other methods to improve emptying and keep intravesical pressures low involves use of reflex voiding with suprapubic tapping and catheterization, utilizing either intermittent or indwelling catheters. Intermittent catheterization is performed by the patient or carers 4–6 times a day. The suitability of this depends on correct aseptic technique, good hand function, motivation, and adequate frequency to ensure bladder volumes of less than 400 mL.[5] There is a significant risk of urinary tract infection in patients who are unable to empty their bladder, and intermittent catheterization may be suitable in these patients. Complications include urethral trauma, false passages, and urine infections. Occasionally, indwelling catheters may be the only practical option in patients with poor hand function not suitable for surgery. These should be avoided long term due to their risk of infection, trauma, and malignant change in the bladder.[14]

Bladder rehabilitation techniques using electrical and magnetic stimulation both externally and intravesically have been shown to have benefits, albeit primarily in pilot studies with small cohorts of patients.[15] There is a need for larger studies to further evaluate this as a treatment option. Where conservative measures have failed, more invasive treatment options are used. Procedures to decrease detrusor contractility include botulinum toxin injection into the detrusor, cystoplasty, and bladder autoaugmentation. Only sacral neuromodulation has been used to increase detrusor contractility. In patients with sphincteric incontinence, sphincter augmentation, artificial urinary sphincter, and bladder neck/urethral reconstruction are valid interventions, but only where detrusor function is under control and bladder pressures are low. Finally, procedures to decrease sphincteric resistance include an external sphincterotomy, urethral stenting, and botulinum toxin injection into the sphincter.

In patients with increased intravesical pressures who are able to empty the bladder, bladder augmentation by replacing or increasing the bladder capacity and thereby reducing intravesical pressure is a well established treatment. A Clam cystoplasty incorporates small intestine into a small contracted bladder. It must be noted that patients are often young, so long-term complications in particular need to be carefully considered. These include recurrent infection, stone formation, metabolic disturbance, perforation, and potential malignant changes.[16] Nevertheless, success rates at 5 years are in excess of 90%.[17] Beyond bladder augmentation, urinary diversion may be considered in order to protect the upper urinary tract, especially in the context of high detrusor pressures without an adequate method of urethral emptying. This should be a continent diversion primarily, although incontinent diversions may be appropriate in some patients where catheterization is not possible.

Of increasing use in patients refractory to conservative and medical management but prior to significant surgery is sacral nerve stimulation or sacral neuromodulation. First described by Schmidt and Tanagho in 1979, the technique stimulates afferents at the sacral level in order to reduce detrusor overactivity.[18] Success rates are in the region of 60%–70%, and this technique may be effective for overactive and underactive detrusor function.[19]

In patients with sphincteric incontinence, techniques to increase outlet resistance may be employed only if bladder pressures are low. The least invasive of these are bulking agents, but their success rates are in the region of 20%–50%.[20] The artificial urinary sphincter has the highest success rate of around 70%, although the procedure suffers from the complications listed for a foreign body implant and requires revision after a number of years.[21]

Lastly, procedures to decrease sphincteric resistance include sphincterotomy and urethral stents. External sphincterotomy is the gold standard for treating detrusor sphincter dyssynergia and often needs repeating. Stents may be temporary (Memokath®) or permanent (Urolume®). Complications include encrustation, migration, development of autonomic dysreflexia, and subsequent stricture formation.[22]

For patients in whom pharmacological treatment is not efficacious or is poorly tolerated, botulinum toxin is often considered before undertaking invasive surgery. It may be used to reduce detrusor overactivity or to relax the external urinary sphincter in detrusor sphincter dyssynergia. The remainder of this review considers the mechanism of action and evidence for botulinum toxin in the treatment of these two conditions.

Types of botulinum toxin

The botulinum toxins (BTX) are the most potent naturally occurring neurotoxins known to man. BTX derives from the Gram-positive coccus *Clostridium botulinum,* and causes a flaccid paralysis of striated muscle by blocking acetylcholine release at the presynapse. First approved by the US Food and Drug Administration in 1989 for the treatment of strabismus, blepharospasm, and hemifacial spasm, its applications have developed significantly since.

There are seven distinct structural serotypes of BTX, ranging from BTX-A to BTX-G. BTX-A is most commonly used in the management of lower urinary tract symptoms. Occasionally, BTX-B has been used in cases resistant

to BTX-A.[23] BTX-A was the first licensed serotype in clinical use under the trade name Botox® (Allergan Pharmaceuticals, Irvine, CA), but other brands also exist, including Dysport® (Ipsen Biopharm Ltd, Slough, UK), Xeomin® (Merz Pharmaceuticals UK Ltd, Hertfordshire, UK), Prosigne®(Lanzhou Biological Products, Lanzhou, China) and PurTox® (Mentor Corporation, Madison, WI). Although all the same serotype, the manufacturing process creates different fragments of the toxin causing biochemical differences. This accounts for the variations in dose, efficacy, duration of effect, and safety profile of the different preparations. OnabotulinumtoxinA, or Botox, is widely studied for its use within the urinary tract. It is approved in approximately 75 countries worldwide and in particular for neurogenic detrusor overactivity secondary to multiple sclerosis and spinal cord injury. Its use for other variations of lower urinary tract dysfunction takes place "off license".

BTX-A in the urinary tract was first described by Dykstra et al in 1988, who injected it into the external urinary sphincter to treat detrusor sphincter dyssynergia in patients with spinal cord injury.[24] Subsequently, Schurch et al reported its use in the treatment of neurogenic detrusor overactivity in 12 patients with spinal cord injury.[25] Its use has since expanded in the management of lower urinary tract symptoms associated with idiopathic detrusor overactivity,[26] bladder outflow obstruction,[27] and painful bladder syndrome/interstitial cystitis.

Mechanism of action of BTX

In order to achieve neurotransmitter exocytosis, plasma membrane proteins are required to bind to the synaptic vesical membrane causing depolarization and calcium influx to trigger release of the neurotransmitter. BTX disrupts the soluble N-ethylmaleimide-sensitive factor attachment protein receptor complex which is critical in this process. This prevents acetylcholine release at somatic and autonomic presynaptic nerve terminals and subsequent lack of stimulation at postsynaptic receptors causing neuromuscular blockade.[28] The potency of the toxin is based on its high selectivity when injected into the detrusor muscle. The effect is not permanent due to lack of neuronal death, and the toxin gradually becomes inactive and is cleared, accounting for return of muscular function.

It is difficult to explain the efficacy of BTX by simple acetylcholine blockage and detrusor paralysis alone. More evidence is still emerging, but BTX has been shown to lead to a decrease in the number of suburothelial afferent neurons expressing purinergic receptors, in particular the $P2X_3$ and TRPV1 receptors.[29] Other proposed actions on the afferent system include inhibition of release of neurotransmitters including ATP, acetylcholine, and substance P from the urothelium.[30] BTX treatment has also been shown to decrease nerve growth factor which could lead to reduced C-fiber hyperexcitability.

OnabotulinumtoxinA for neurogenic detrusor overactivity

BTX-A has been investigated using either Botox (onabotulinumtoxinA) or Dysport (abobotulinumtoxinA), with 10 high-level studies (level 1 or 2, Oxford classification) assessing management of neurogenic detrusor overactivity. When looking at all forms of studies, onabotulinumtoxinA is more widely investigated and is the only licensed preparation.[31] Schurch et al first published on the use of onabotulinumtoxinA in 19 spinal cord injury patients with neurogenic detrusor overactivity in 2000.[25] They showed significant improvements in patient symptoms as well as in urodynamic parameters.

In 2004, Rietz et al reported on a multicenter, open-label study in which 300 U of abobotulinumtoxinA was injected at 30 sites within the detrusor muscle in patients with neurogenic detrusor overactivity. Rietz et al, like Schurch et al, reported significant urodynamic improvements. Seventy-three percent of incontinent patients were continent by 12 weeks and, of interest, 28% of patients also on antimuscarinics had discontinued these by this point.[32] In the same year, Giannantoni et al published the first controlled study of onabotulinumtoxinA in patients with neurogenic detrusor overactivity. Patients were randomized to either 300 U of intravesical onabotulinumtoxinA or to 0.6 μmol/L of intravesical resiniferatoxin.[33] They showed that those receiving onabotulinumtoxinA had superior improvements in symptoms of incontinence, need for catheterization, and maximum cystometric capacity over resiniferatoxin.

Subsequently, the first randomized, placebo-controlled study of onabotulinumtoxinA was published by Schurch et al in 2005.[34] Significant improvements were found in patient-reported outcomes for return to continence, daily catheterization, compliance, and urodynamic findings of maximum cystometric capacity, maximum detrusor pressure (pdet max), and reflex volume (volume at first involuntary contraction) after 200 U and 300 U compared with placebo. A subsequent paper reported on improvements in health-related quality of life.[35]

A recently published, large, randomized, double-blind, placebo-controlled Phase III study compared

onabotulinumtoxinA with placebo in patients with neurogenic detrusor overactivity secondary to multiple sclerosis or spinal cord injury. Cruz et al compared 92 patients receiving placebo with 92 who received 200 U and 91 who received 300 U.[36] By 2 weeks, both onabotulinumtoxinA groups reported significant improvement in urgency incontinence episodes per week. There were also significant improvements in maximum cystometric capacity and pdet max pressure during the first overactive contraction. The median time to need for retreatment was 42 weeks for both treatment groups compared with 16 weeks for placebo. It must be noted that in patients not performing intermittent catheterization, an increase in post void residual was found in 12% of the placebo group, compared with 30% and 40% in the 200 U and 300 U groups, respectively. One patient who received 300 U reported a serious adverse event of muscular weakness.

Ginsberg et al published a similar study comparing onabotulinumtoxinA and placebo, whereby 149 patients received placebo, 135 received 200 U onabotulinumtoxinA, and 132 received 300 U. Both dose preparations led to significant improvements in urgency incontinence episodes at 6 weeks.[37] Beneficial effects were seen to last for up to 36.6 weeks in those treated with either botulinum toxin dose compared with 13 weeks for placebo. Herschorn et al reported considerable reduction in patient-reported urinary incontinence in 28 patients receiving 300 U of onabotulinumtoxinA compared with 29 receiving placebo.[38] The time to request for retreatment was up to 36 weeks. Both pdet max and maximum cystometric capacity were significantly improved in patients after treatment at 6 weeks, with improved urodynamic parameters at week 24.

In a study investigating lower doses of 50 U, 100 U, and 200 U versus placebo, the group receiving 200 U showed significant symptom improvement when compared with placebo.[39] Those receiving 50 U and 100 U were not significantly different to placebo, but this may have been a consequence of small study numbers.

Over the years, the injection technique has changed slightly. Injections are given into the detrusor muscle or suburethrally via a flexible cystoscope under local anesthetic. Initial studies used a rigid cystoscope and general anesthetic. It was also proposed that intravesical injections should exclude the trigone of the bladder due to the theoretical risk of vesicoureteric reflux. However, Abdel-Meguid et al have shown that administration of 100 U and 200 U into the trigone and detrusor muscle respectively, compared with 300 U exclusively into the detrusor, reduced leak episodes and increased reflex volumes.[40] Furthermore, there was no evidence of vesicoureteric reflux which has made trigonal injections acceptable.

The high-level literature available suggests that treatment of neurogenic detrusor overactivity with onabotulinumtoxinA is now no longer reserved as a later option, but moreso is becoming standard practice with increasing understanding of dosing, efficacy, and side effect profiles. The difference in outcomes with regards to number of injections as well as depth of injection is not well studied.

OnabotulinumtoxinA for detrusor sphincter dyssynergia

In total, only two level 1 studies (Oxford classification) have investigated onabotulinumtoxinA in the treatment of detrusor sphincter dyssynergia.[31] AbobotulinumtoxinA has only been described in two level 3 studies. The use of onabotulinumtoxinA 100 U has shown improvements in post void residual by 60% in one randomized controlled trial[41] and 15% in another.[42] The latter found no significant benefit over placebo. Another nonrandomized study by Kuo has shown 60% satisfaction in patients with detrusor sphincter dyssynergia.[43] Given the discrepant findings and nonpermanent effect, onabotulinumtoxinA needs to be used in well chosen patients with detrusor sphincter dyssynergia.

Adverse events

Treatment-related adverse events secondary to intradetrusor onabotulinumtoxinA injection are few. They can be divided into local and systemic events. Commonly occurring local events include pain, infection, and hematuria, which are often related to the procedure rather than to the toxin. The risk of temporary increase in post void residual or urinary retention is well documented, and therefore patients need to be willing and able to perform intermittent self-catheterization if not already doing so.

Systemic events occur due to migration of toxin beyond the detrusor muscle and can cause muscle weakness or hypoasthenia. Reports of hypoasthenia were first reported by Wyndaele in 2002.[44,45] The incidence of severe adverse events in high-level studies in patients receiving botulinum toxin is low. When reviewing 26 studies for isolated cases of hypoasthenia secondary to onabotulinumtoxinA, only two reported a rate of 2%–15%.[46,47] The rate of urinary tract infection is reported at 21%–32% and injection-associated pain at 10%.[34] However, it must be noted that the majority of cases of hypoasthenia are transient and mild. There are no reports of adults requiring hospitalization and only

a few reports of significant disruption to patient quality of life.[44,48,49]

Quality of life

One of the main aims for management of patients with NLUTD is improvement in quality of life, which plays a significant role in overall treatment outcomes. There are various factors influencing quality of life in addition to symptom management. These include family support, finance, education, self-esteem, coping mechanisms, and the living environment.[50] There is no quality of life questionnaire designed specifically for NLUTD. Qualiveen® is a specific tool to assess quality of life in patients with spinal cord injury and multiple sclerosis which has been validated. More commonly, generic questionnaires, such as the Incontinence Quality of Life Instrument (I-QOL) and Short Form 36 Health Survey Questionnaire are used. From the high-level studies, Schurch et al and Cruz et al have shown significant improvements in I-QOL with onabotulinumtoxinA 200 U and 300 U compared with placebo.[35,36] A longer-term study by Khan et al has reported that patients with multiple sclerosis continued to enjoy improvements in quality of life with repeated injections of onabotulinumtoxinA as assessed by the Urogenital Distress Inventory and Incontinence Impact Questionnaire 7.[51] The emphasis on quality of life and the subsequent influence on patient adherence and uptake is paramount in assessing long-term success from this therapy.

Future directions

From the above data, it is clear that although onabotulinumtoxinA has received a license for use in neurogenic detrusor overactivity more work is still required to understand fully the mechanisms of action, patient selection, and efficacy. There is little data on which patients improve most with BTX therapy. It has been suggested that a maximum detrusor pressure > 110 cm H_2O may be a predictor of poor response.[52] Histological assessment has shown that bladders post BTX injection have less fibrosis than BTX-naïve bladders.[53] Also, in this study, responders to BTX therapy showed a trend towards less fibrosis than nonresponders. Because it has been shown that BTX does not itself lead to fibrosis,[54] it can be assumed that there may be a limit to the amount of fibrosis treatable with BTX. Another reason for long-term failure may be the formation of antibodies to BTX. This has been reported in one study to occur in eight of 25 patients; of these, four patients showed a strong antibody reaction and four showed an equivocal reaction.[55] Although the persistence and significance of the antibody has been debated, one study has shown return of efficacy for BTX-A after proven resistance.[56] Another option in these patients is the use of BTX-B.

Future work now needs to concentrate on perfecting injection parameters. It is not known whether the number and volume of injections has an impact on efficacy outcomes. The depth of injection also needs investigating. Finally, a better understanding of the mechanism of action may allow better selection of patients to reduce failure rates.

Conclusion

Use of onabotulinumtoxinA in NLUTD is clearly a well established treatment option with good outcomes and minimal adverse effects in a group of patients that is otherwise difficult to manage. OnabotulinumtoxinA is more widely studied than any other preparation of BTX-A currently available. Despite the focus on patients with NLUTD, there is high-level evidence available and increasing frequency of use, albeit "off license", in other forms of lower urinary tract dysfunction, ie, idiopathic detrusor overactivity, and less so in bladder outflow obstruction and painful bladder syndrome.

Dosing studies suggest 200 U in neurogenic detrusor overactivity is efficacious and a suitable starting point.[36] However, the relationship between increased dose and increased risk of adverse events would suggest treatment dose and regime be tailored to the individual patient. More emphasis must be placed on ensuring patient quality of life as a key primary outcome. Significant adverse events have been shown to be minimal and, if present, transient and self-limiting. A recent systematic review reported that, of 1025 patients receiving onabotulinumtoxinA, the reported incidence of hypoasthenia was only five (0.005%).[31]

With regards to long-term outcomes, use of BTX-A has been shown to maintain efficacy of treatment for up to eight injections.[57,58] It is not clear which patients will develop resistance to treatment, and questions have been raised as to the risk of antibody development against BTX-A. Schulte-Baukloh et al reported on formation of antibodies to onabotulinumtoxinA in eight patients from a cohort of 25 patients with neurogenic detrusor overactivity.[55] However, the significance of this in relation to treatment failure was not convincingly demonstrated. Early evidence alludes to a change in the thinking regarding trigonal injection. This, along with number and volume of injections, highlights areas requiring further study, with a potential for further beneficial outcomes.

In summary, onabotulinumtoxinA use in the treatment of NLUTD has become common practice and with strong

supporting evidence. How best to utilize it and its place in the treatment of other variations of bladder dysfunction requires ongoing study, but is fast evolving.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Gerridzen RG, Thijssen AM, Dehoux E. Risk factors for upper tract deterioration in chronic spinal cord injury patients. *J Urol*. 1992;147(2):416–418.
2. Burns AS, Rivas DA, Ditunno JF. The management of neurogenic bladder and sexual dysfunction after spinal cord injury. *Spine (Phila Pa)*. 1976;26(Suppl 24):S129–S136.
3. Hackler RH. A 25-year prospective mortality study in the spinal cord injured patient: comparison with the long-term living paraplegic. *J Urol*. 1977;117(4):486–488.
4. Lidal IB, Snekkevik H, Aamodt G, Hjeltnes N, Biering-Sorensen F, Stanghelle JK. Mortality after spinal cord injury in Norway. *J Rehabil Med*. 2007;39(2):145–151.
5. Pannek J, Stohrer M, Blok B, et al. *Guidelines on Neurogenic Lower Urinary Tract Dysfunction*. Arnhem, The Netherlands: European Association of Urology; 2011.
6. Marrie RA, Cutter G, Tyry T, Vollmer T, Campagnolo D. Disparities in the management of multiple sclerosis-related bladder symptoms. *Neurology*. 2007;68(23):1971–1978.
7. Satar N, Bauer SB, Shefner J, Kelly MD, Darbey MM. The effects of delayed diagnosis and treatment in patients with an occult spinal dysraphism. *J Urol*. 1995;154(2 Pt 2):754–758.
8. Madersbacher H. The various types of neurogenic bladder dysfunction: an update of current therapeutic concepts. *Paraplegia*. 1990;28(4):217–229.
9. Rickwood AM. Assessment and conservative management of the neuropathic bladder. *Semin Pediatr Surg*. 2002;11(2):108–119.
10. Madhuvrata P, Singh M, Hasafa Z, Abdel-Fattah M. Anticholinergic drugs for adult neurogenic detrusor overactivity: a systematic review and meta-analysis. *Eur Urol*. February 25, 2012. [Epub ahead of print.]
11. Chancellor MB, Anderson RU, Boone TB. Pharmacotherapy for neurogenic detrusor overactivity. *Am J Phys Med Rehabil*. 2006;85(6):536–545.
12. Stohrer M, Pannek J. Surgery to improve reservoir function. In: Corcos J, Schick E, editors. *Textbook of the Neuropathic Bladder*. 2nd ed. London, UK: Informa Healthcare; 2008.
13. Linsenmeyer TA, Horton J, Benevento J. Impact of alpha1-blockers in men with spinal cord injury and upper tract stasis. *J Spinal Cord Med*. 2002;25(2):124–128.
14. Talbot HS, Mahoney EM, Jaffee SR. The effects of prolonged urethral catheterization. I. Persistence of normal renal structure and function. *J Urol*. 1959;81(1):138–145.
15. McClurg D, Ashe RG, Marshall K, Lowe-Strong AS. Comparison of pelvic floor muscle training, electromyography biofeedback, and neuromuscular electrical stimulation for bladder dysfunction in people with multiple sclerosis: a randomized pilot study. *Neurourol Urodyn*. 2006;25(4):337–348.
16. Greenwell TJ, Venn SN, Mundy AR. Augmentation cystoplasty. *BJU Int*. 2001;88(6):511–525.
17. Khastgir J, Hamid R, Arya M, Shah N, Shah PJ. Surgical and patient reported outcomes of 'clam' augmentation ileocystoplasty in spinal cord injured patients. *Eur Urol*. 2003;43(3):263–269.
18. Schmidt RA, Tanagho EA. Feasibility of controlled micturition through electric stimulation. *Urol Int*. 1979;34(3):199–230.
19. Chaabane W, Guillotreau J, Castel-Lacanal E, et al. Sacral neuromodulation for treating neurogenic bladder dysfunction: clinical and urodynamic study. *Neurourol Urodyn*. 2011;30(4):547–550.
20. Bennett JK, Green BG, Foote JE, Gray M. Collagen injections for intrinsic sphincter deficiency in the neuropathic urethra. *Paraplegia*. 1995;33(12):697–700.
21. Chartier KE, Genevois S, Game X, et al. Treatment of neurogenic male urinary incontinence related to intrinsic sphincter insufficiency with an artificial urinary sphincter: a French retrospective multicentre study. *BJU Int*. 2011;107(3):426–432.
22. Reynard JM, Vass J, Sullivan ME, Mamas M. Sphincterotomy and the treatment of detrusor-sphincter dyssynergia: current status, future prospects. *Spinal Cord*. 2003;41(1):1–11.
23. Pistolesi D, Selli C, Rossi B, Stampacchia G. Botulinum toxin type B for type A resistant bladder spasticity. *J Urol*. 2004;171(2 Pt 1):802–803.
24. Dykstra DD, Sidi AA, Scott AB, Pagel JM, Goldish GD. Effects of botulinum A toxin on detrusor-sphincter dyssynergia in spinal cord injury patients. *J Urol*. 1988;139(5):919–922.
25. Schurch B, Schmid DM, Stohrer M. Treatment of neurogenic incontinence with botulinum toxin A. *N Engl J Med*. 2000;342(9):665.
26. Kuo HC. Urodynamic evidence of effectiveness of botulinum A toxin injection in treatment of detrusor overactivity refractory to anticholinergic agents. *Urology*. 2004;63(5):868–872.
27. Maria G, Brisinda G, Civello IM, Bentivoglio AR, Sganga G, Albanese A. Relief by botulinum toxin of voiding dysfunction due to benign prostatic hyperplasia: results of a randomized, placebo-controlled study. *Urology*. 2003;62(2):259–264.
28. Montecucco C, Molgo J. Botulinal neurotoxins: revival of an old killer. *Curr Opin Pharmacol*. 2005;5(3):274–279.
29. Apostolidis A, Popat R, Yiangou Y, et al. Decreased sensory receptors P2X3 and TRPV1 in suburothelial nerve fibers following intradetrusor injections of botulinum toxin for human detrusor overactivity. *J Urol*. 2005;174(3):977–982.
30. Lawrence GW, Aoki KR, Dolly JO. Excitatory cholinergic and purinergic signaling in bladder are equally susceptible to botulinum neurotoxin a consistent with co-release of transmitters from efferent fibers. *J Pharmacol Exp Ther*. 2010;334(3):1080–1086.
31. Mangera A, Andersson KE, Apostolidis A, et al. Contemporary management of lower urinary tract disease with botulinum toxin A: a systematic review of botox (onabotulinumtoxinA) and dysport (abobotulinumtoxinA). *Eur Urol*. 2011;60(4):784–795.
32. Reitz A, Stohrer M, Kramer G, et al. European experience of 200 cases treated with botulinum-A toxin injections into the detrusor muscle for urinary incontinence due to neurogenic detrusor overactivity. *Eur Urol*. 2004;45(4):510–515.
33. Giannantoni A, Di Stasi SM, Stephen RL, Bini V, Costantini E, Porena M. Intravesical resiniferatoxin versus botulinum-A toxin injections for neurogenic detrusor overactivity: a prospective randomized study. *J Urol*. 2004;172(1):240–243.
34. Schurch B, de Sèze M, Denys P, et al; Botox Detrusor Hyperreflexia Study Team. Botulinum toxin type A is a safe and effective treatment for neurogenic urinary incontinence: results of a single treatment, randomized, placebo controlled 6-month study. *J Urol*. 2005;174(1):196–200.
35. Schurch B, Denys P, Kozma CM, Reese PR, Slaton T, Barron RL. Botulinum toxin A improves the quality of life of patients with neurogenic urinary incontinence. *Eur Urol*. 2007;52(3):850–858.
36. Cruz F, Herschorn S, Aliotta P, et al. Efficacy and safety of onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity: a randomised, double-blind, placebo-controlled trial. *Eur Urol*. 2011;60(4):742–750.
37. Ginsberg D, Gousse A, Keppenne V, et al. Phase 3 efficacy and safety study of onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity. [Abstract]. Presented at the 2011 Annual Meeting of the American Urological Association, May 14–19, 2011, Washington, DC.
38. Herschorn S, Gajewski J, Ethans K, et al. Efficacy of botulinum toxin A injection for neurogenic detrusor overactivity and urinary incontinence: a randomized, double-blind trial. *J Urol*. 2011;185(6):2229–2235.

39. Apostolidis A, Mourad S, Thompson C, Yan X, Haag-Molkenteller C. A dose-exploration study of the efficacy and safety of onabotulinumtoxina in patients with urinary incontinence due to neurogenic detrusor overactivity. International Continence Society meeting, August 29–September 2, 2011, Glasgow, Scotland.
40. Abdel-Meguid TA. Botulinum toxin-A injections into neurogenic overactive bladder – to include or exclude the trigone? A prospective, randomized, controlled trial. *J Urol*. 2010;184(6):2423–2428.
41. de Sèze M, Petit H, Gallien P, et al. Botulinum a toxin and detrusor sphincter dyssynergia: a double-blind lidocaine-controlled study in 13 patients with spinal cord disease. *Eur Urol*. 2002;42(1):56–62.
42. Gallien P, Reymann JM, Amarenco G, Nicolas B, de Sèze M, Bellissant E. Placebo controlled, randomised, double blind study of the effects of botulinum A toxin on detrusor sphincter dyssynergia in multiple sclerosis patients. *J Neurol Neurosurg Psychiatry.* 2005;76(12):1670–1676.
43. Kuo HC. Satisfaction with urethral injection of botulinum toxin A for detrusor sphincter dyssynergia in patients with spinal cord lesion. *Neurourol Urodyn*. 2008;27(8):793–796.
44. Wyndaele JJ, Van Dromme SA. Muscular weakness as side effect of botulinum toxin injection for neurogenic detrusor overactivity. *Spinal Cord*. 2002;40(11):599–600.
45. De Laet K, Wyndaele JJ. Adverse events after botulinum A toxin injection for neurogenic voiding disorders. *Spinal Cord*. 2005;43(7):397–399.
46. Pannek J, Gocking K, Bersch U. Long-term effects of repeated intradetrusor botulinum neurotoxin A injections on detrusor function in patients with neurogenic bladder dysfunction. *BJU Int*. 2009;104(9):1246–1250.
47. Kalsi V, Gonzales G, Popat R, et al. Botulinum injections for the treatment of bladder symptoms of multiple sclerosis. *Ann Neurol*. 2007;62(5):452–457.
48. Bauer RM, Gratzke C, Roosen A, et al. Patient-reported side effects of intradetrusor botulinum toxin type A for idiopathic overactive bladder syndrome. *Urol Int*. 2011;86(1):68–72.
49. Stoehrer M, Wolff A, Kramer G, et al. Treatment of neurogenic detrusor overactivity with botulinum toxin A: the first seven years. *Urol Int*. 2009;83(4):379–385.
50. Whiteneck G, Meade MA, Dijkers M, Tate DG, Bushnik T, Forchheimer MB. Environmental factors and their role in participation and life satisfaction after spinal cord injury. *Arch Phys Med Rehabil*. 2004;85(11):1793–1803.
51. Khan S, Game X, Kalsi V, et al. Long-term effect on quality of life of repeat detrusor injections of botulinum neurotoxin-A for detrusor overactivity in patients with multiple sclerosis. *J Urol*. 2011;185(4):1344–1349.
52. Sahai A, Khan MS, Le Gall N, Dasgupta P; GKT Botulinum Study Group. Urodynamic assessment of poor responders after botulinum toxin-A treatment for overactive bladder. *Urology*. 2008;71(3):455–459.
53. Comperat E, Reitz A, Delcourt A, Capron F, Denys P, Chartier-Kastler E. Histologic features in the urinary bladder wall affected from neurogenic overactivity – a comparison of inflammation, oedema and fibrosis with and without injection of botulinum toxin type A. *Eur Urol*. 2006;50(5):1058–1064.
54. Apostolidis A, Jacques TS, Freeman A, et al. Histological changes in the urothelium and suburothelium of human overactive bladder following intradetrusor injections of botulinum neurotoxin type A for the treatment of neurogenic or idiopathic detrusor overactivity. *Eur Urol*. 2008;53(6):1245–1253.
55. Schulte-Baukloh H, Bigalke H, Miller K, et al. Botulinum neurotoxin type A in urology: antibodies as a cause of therapy failure. *Int J Urol*. 2008;15(5):407–415.
56. Pistolesi D, Giannarini G, Stampacchia G, Selli C. Should we stop using botulinum neurotoxin type a in patients with neurogenic detrusor overactivity after development of secondary resistance? *Eur Urol*. 2011;60(4):872–873.
57. Del Popolo G, Filocamo MT, Li Marzi V, et al. Neurogenic detrusor overactivity treated with English botulinum toxin a: 8-year experience of one single centre. *Eur Urol*. 2008;53(5):1013–1019.
58. Sahai A, Dowson C, Khan MS, Dasgupta P. Repeated injections of botulinum toxin-A for idiopathic detrusor overactivity. *Urology*. 2010;75(3):552–558.