UIJ UroToday International Journal®

www.urotodayinternationaljournal.com
Volume 2 - December 2009

Minimally Invasive Therapy for Neurogenic Detrusor Overactivity: A Review

Karl-Erik Andersson,[1] Roger Dmochowski,[2] Alan J. Wein[3]

[1]Wake Forest Institute for Regenerative Medicine, Wake Forest University School of Medicine, Winston-Salem, NC, USA; [2]Department of Urology, Vanderbilt University Medical Center, Nashville, TN, USA; [3]Division of Urology, University of Pennsylvania Health System, Philadelphia, PA, USA

Submitted October 8, 2009 - Accepted for Publication November 2, 2009

ABSTRACT

Urinary incontinence secondary to neurogenic detrusor overactivity (NDO) is a common problem in patients with neurologic pathology. Patients with NDO are at increased risk for recurrent urinary tract infection and renal damage, especially due to high intravesical pressures. They may also experience urinary urgency, frequency, and incontinence, which are all factors that negatively affect quality of life. Oral antimuscarinic agents are considered first-line pharmacologic therapy, but their use may be limited by adverse effects and result in poor compliance and adherence. Surgical augmentation of the bladder is a rare final alternative when other attempts to restore continence have failed. However, there are other less invasive treatment options that are currently available or undergoing research. These options include transdermal or intravesical administration of antimuscarinics, intravesical administration of other agents (including vanilloids and botulinum toxins A and B), and electrical stimulation. The available alternatives have demonstrated varying degrees of efficacy and are all minimally invasive, allowing surgery to be avoided where possible. However, neither vanilloid nor botulinum toxin therapy is approved by the United States Food and Drug Administration for treatment of detrusor overactivity. Treatment should always begin with the most reversible forms of therapy and progress to more complex options.

KEYWORDS: Antimuscarinics; Botulinum toxin; Neurogenic detrusor overactivity; Neuromodulation

CORRESPONDENCE: Karl-Erik Andersson, MD, PhD, Wake Forest Institute for Regenerative Medicine, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157 (Karl-Erik.Andersson@med.lu.se)

CITATION: *UroToday Int J*. 2009 Dec;2(6). doi:10.3834/uij.1944-5784.2009.12.10

INTRODUCTION

Damage to supraspinal structures involved in micturition control and/or to the spinal cord above the sacral level may result in detrusor overactivity [1,2]. Such neurogenic detrusor overactivity (NDO) is a common problem in patients with neurologic pathology from a diversity of causes, including spinal cord injury, multiple sclerosis (MS), and Parkinson's disease (PD) (Table 1). NDO may also occur in a significant proportion of patients with diabetic neuropathy [3,4]. Patients with NDO frequently experience urinary frequency, urgency, and incontinence. Incomplete voiding, elevated intravesical pressure, and catheter use, which may be associated with NDO, increase the risk for recurrent urinary tract infection [5]. Renal damage may be a concern due to high intravesical pressures associated with detrusor sphincter dyssynergia. In addition, urinary urgency and incontinence are embarrassing for patients, can result in loss of independence and/or institutionalization, and have a significant impact on quality of life (QOL) [6]. Therefore, effective management is crucial.

Patients with NDO represent only a small proportion of the

UroToday International Journal®

review

Minimally Invasive Therapy for Neurogenic Detrusor Overactivity: A Review

Table 1. Neurologic Conditions That May Result in Urinary Tract Dysfunction.

doi: 10.3834/uij.1944-5784.2009.12.10t1

Conditions Affecting the Brain
Cerebrovascular accident
Intracranial neoplasms
Parkinson's disease
Dementia
Shy-Drager syndrome (multiple system atrophy)
Cerebellar ataxia
Cerebral palsy
Conditions Affecting the Spinal Cord
Spinal cord injury
Multiple sclerosis
Intervertebral disc disease
Ankylosing spondylosis
Guillain-Barré syndrome
Tabes dorsalis
Pernicious anemia
Acquired immune deficiency syndrome
Tropical spastic paraparesis
Transverse myelitis
Lyme disease
Herpes zoster
Poliomyelitis
Myelomeningocele
Tethered cord syndrome and short filum terminale
Conditions Affecting the Peripheral Nervous System
Pelvic plexus injury (pelvic surgery or pelvic trauma)
Diabetic neuropathy
Other Neuromuscular Conditions Affecting Voiding Function
Myasthenia gravis

total population of patients with detrusor overactivity, which is a urodynamic diagnosis [7]. There is a paucity of specific clinical data on the effectiveness of therapies in patients with NDO. Therefore, efficacy has been largely inferred from studies of patients with nonneurogenic or idiopathic detrusor overactivity (IDO) [7], or of patients with the symptom-based diagnosis of overactive bladder (OAB) who may or may not have detrusor overactivity [8]. This approach has limitations because the treatment goals are different between the two conditions.

The most extreme of the treatment options available for NDO is surgical augmentation of the bladder to reduce pressure and overactivity. This is usually the final alternative when other attempts to restore continence have failed. In addition to the general risks associated with any surgical intervention, bladder surgery is a permanent procedure that commits patients to catheterization for the rest of their lives. Therefore, less invasive treatment options are preferable in patients with NDO for whom first-line therapy is not successful. Many patients with NDO use clean intermittent catheterization (CIC) to overcome voiding dysfunction, and treatment of NDO to improve urine retention during the bladder-filling phase in such patients is an important goal of NDO therapy. Although no single approach is usually perfect, it is important to achieve patient satisfaction and avoid adverse events. The present review details minimally invasive treatment approaches for patients with NDO.

Treatment Options

The goals of therapy for NDO are achievement of low bladder pressures, minimization of infection risk and avoidance of renal damage, maintenance of continence, improvement of QOL, and support of independent living and rehabilitation [9]. Treatment options for IDO need to reduce urgency, frequency, and urgency urinary incontinence without causing greatly increased residual urine volume. In contrast, many patients with NDO already need to use CIC. In these patients, retention of urine is an important goal of treatment, with the aim of preventing any urine leakage in between CIC.

Antimuscarinic Agents

Oral antimuscarinic (anticholinergic) agents are recognized as safe and effective in the treatment of OAB and detrusor overactivity [10,11]. Current guidelines recommend the use of oral antimuscarinics as first-line pharmacologic therapy for the management of urinary incontinence secondary to detrusor overactivity [7,10].

Antimuscarinic agents competitively inhibit the effects of acetylcholine (ACh) at postjunctional muscarinic receptors on detrusor smooth muscle and on other structures in the bladder wall or outside the bladder. The detrusor muscle contains mainly type 2 and type 3 muscarinic receptors (M_2 and M_3), with M_3 receptors thought to be the most important for detrusor contraction. The function of M_2 receptors has yet to be clearly defined, but it has been suggested that these might have an indirect role in mediating bladder contractions by enhancing M_3-mediated effects [12,13]. The traditional view has been that the antimuscarinics inhibit voluntary and involuntary bladder

contractions by blocking the muscarinic receptors on the detrusor. This especially may be the case in NDO.

ACh is released from parasympathetic efferent nerves and may also be produced and released from nonneuronal sources, including the urothelium. Muscarinic receptors have been detected on the urothelium and on suburothelial interstitial cells, and the density of these receptors is increased in patients with clinical bladder symptoms [14]. The urothelium/suburothelium is now thought to play a role in bladder sensory mechanisms via activation of local afferent nerves, which monitor the volume of the bladder and the amplitude of bladder contraction [15]. Thus, antimuscarinic agents may reduce detrusor activity and improve bladder capacity via additional mechanisms, including direct inhibition of bladder afferent signaling at the level of the urothelium and suburothelium [16,17].

Six antimuscarinic agents have been approved by the United States Food and Drug Administration (FDA) for the treatment of OAB: darifenacin, fesoterodine, oxybutynin (in transdermal patch, gel, and oral formulations), solifenacin, tolterodine, and trospium chloride. The efficacy of oxybutynin, the most widely used agent and the only agent approved for high-dose administration, is well documented [18]. Fesoterodine is the most recently approved antimuscarinic drug for OAB in the United States (October 2008). Antimuscarinics must be given at an adequate dosage to achieve a therapeutic effect, and may be titrated until clinical improvement is achieved or drug-induced side effects become problematic.

Efficacy. There is ample evidence to support the efficacy of antimuscarinic agents for the treatment of the OAB syndrome and ideopathic detrusor overactivity (IDO). Large, randomized, placebo-controlled studies have demonstrated that patients receiving these agents report significant reductions in urinary frequency, urgency episodes, and urgency urinary incontinence [11,19,20]. A meta-analyses of clinical trials involving over 10,000 patients evaluated antimuscarinic agents together as a whole (including the 5 agents approved prior to 2008) versus placebo in adult patients with OAB, a urodynamic diagnosis of detrusor overactivity (IDO or NDO), or both [19]. Statistically significant improvements were observed: (1) in the number of incontinence episodes per day versus placebo (weighted mean difference [WMD], -0.51; 95% confidence interval [CI], -0.66 to -0.37, representing a reduction of 3 to 5 incontinence episodes per week), and (2) in urinary frequency (WMD, -0.68; 95% CI, -0.84 to -0.52, representing 4 to 6 fewer voids per week) [19]. The clinical benefit of individual antimuscarinic agents that included fesoterodine in patients with OAB was similarly demonstrated in a meta-analysis by Chappel et al [11] and later updated [20]. In these analyses, active treatments were more effective than placebo for mean change in incontinence episodes per day and mean change in micturition frequency per day for all agents evaluated, except trospium chloride which was not reported [20]. Pooled differences in mean changes ranged from 0.4 to 1.1 incontinence episodes per day and from 0.5 to 1.3 micturitions per day [20]. Significant improvements in health-related QOL measures also result from the use of antimuscarinic agents [19-21].

Some differences in efficacy exist between antimuscarinic agents, as seen in comparative studies [11,20]. These differences may be related to variations in the occurrence of treatment-limiting adverse events, route of administration (oral versus transdermal), relative affinities for human muscarinic receptor subtypes, and/or the formulation (immediate release [IR] or extended release [ER]).

Alhasso et al [22] conducted a meta-analysis of controlled trials of antimuscarinic agents in which at least one arm involved nondrug active therapy such as bladder training or electrical stimulation. Symptomatic improvement, including number of incontinence or urgency episodes per day and frequency of micturition, was more common among patients who received an antimuscarinic agent (oxybutynin, tolterodine, or propantheline) versus bladder training (risk ratio [RR], 0.73; 95% CI, 0.59-0.90), and augmenting bladder training with antimuscarinic drug treatment improved response versus bladder training alone (RR, 0.55; 95% CI, 0.32-0.93). It should be noted that the analysis excluded trials that involved patients with neuropathic bladder dysfunction.

Adverse Events. Therapy for detrusor overactivity is usually long term, and the incidence of antimuscarinic-induced adverse events is relatively high. Common adverse events are the expected side effects of antimuscarinic drugs. The side effects are from the blockade of muscarinic receptors in, for example, the salivary gland, colon, and ciliary smooth muscle, and result in dry mouth, constipation, and blurred vision, respectively (Table 1) [23]. Dry mouth (4.1%-29.0%) and constipation (3.3%-14.8%) were the most commonly reported adverse events in phase III clinical studies. Most were mild to moderate in intensity (Table 2) [24-31]. Adverse events may be less common when newer ER or long-acting antimuscarinic preparations are used [11].

Among the more serious potential concerns related to antimuscarinic use is the risk of cardiac adverse effects, particularly increases in heart rate and QT prolongation and induction of polymorphic ventricular tachycardia (torsade de pointes). It should be emphasized that QT prolongation and its consequences are not related to blockade of muscarinic receptors, but rather linked to inhibition of the hERG potassium channel in the heart [32]. Thus, QT prolongation is not a class

doi:10.3834/uij.1944-5784.2009.12.10
ISSN 1944-5792 (print), ISSN 1944-5784 (online)

Table 2. Common Adverse Events (AE) Occurring in Patients Receiving Antimuscarinic Drugs, Summarized from Respective Prescribing Information. doi: 10.3834/uij.1944-5784.2009.12.10t2

Drug [Prescribing Information Reference]	Adverse Event	AE Incidence (% of Patients)	
		Active Treatment	Placebo
Darifenacin [24] 7.5 mg/day;15 mg/day	Dry mouth	20.2; 35.3	8.2
	Constipation	14.8; 21.3	6.2
	Dyspepsia	2.7; 8.4	2.6
Fesoterodine [25] 4 mg/day; 8 mg/day	Dry mouth	18.8; 34.6	7.0
	Constipation	4.2; 6.0	2.0
Oxybutynin oral ER [26] 5–30 mg/day	Dry mouth	61	NR
	Constipation	13	NR
	Somnolence	**12**	**NR**
	Headache	10	NR
	Diarrhea	9	NR
	Nausea	9	NR
	Blurred vision	8	NR
	Asthenia	7	NR
	Dizziness	7	NR
	Pain	7	NR
	Dizziness	6	NR
	Dry eyes	6	NR
	Rhinitis	6	NR
	Urinary tract infection	5	NR
Oxybutynin transdermal patch [27] 3.9 mg/day[a,b]	Application site pruritus	14.0–16.8	4.3–6.1
	Dry mouth	4.1–9.6	1.7–8.3
	Application site erythema	5.6–8.3	1.7–2.3
Oxybutynin transdermal gel [28] 10%	Dry mouth	7.5	2.8
	Urinary tract infection	**6.9**	**4.3**
	Application site reactions	5.4	1.0
	Upper respiratory tract infection	5.4	5.0
Solifenacin ER [29] 5 mg/day; 10 mg/day	Dry mouth	10.9; 27.6	4.2
	Constipation	5.4; 13.4	2.9
Tolterodine ER [30] 4 mg/day	Dry mouth	23	8
	Constipation	6	4
	Headache	6	4
Trospium chloride ER [31] 60 mg/day	Dry mouth	11.1	3.7
	Constipation	9.0	1.7
	Urinary tract infection	7.3	4.9

Abbreviations: ER, extended release; AE, adverse event; NR, not reported.
[a]Data were reported regardless of causality for all drugs except oxybutynin transdermal patch, where the data reported were for AEs judged by the investigator as possibly, probably, or definitely treatment-related; [b]Ranges shown for AE incidence for oxybutynin transdermal patch and matching placebo represent data reported in prescribing information from 2 studies.

effect of antimuscarinics. M_2 receptors play a prominent role in cardiac function, and the use of antimuscarinic drugs with M_2 receptor-blocking activity may increase resting heart rate [33]. Available data from clinical studies indicate that recommended therapeutic dosages of antimuscarinic agents do not substantially increase the risk of cardiac adverse events [10]. However, post-marketing surveillance data for OAB antimuscarinic agents include reports of adverse cardiac events, including tachycardia, arrhythmia, torsade de pointes, and peripheral edema [24,26,29-31].

All 5 muscarinic receptors are found in the brain, and M_1 and M_2 receptors appear to play a major role in memory and cognitive function [23]. Antimuscarinic agents differ in their propensity to cross the blood-brain barrier, based in large part on their physicochemical properties. Nevertheless, blood-brain barrier integrity can decline in old age or as a result of both neurodegenerative (eg, Alzheimer's and PD) and inflammation-related diseases (eg, vascular dementia and MS) [34]. Such changes present a challenge for successful antimuscarinic treatment of OAB in these patients [35,36].

Adverse events associated with antimuscarinic therapy are problematic in patients with NDO and can result in drug discontinuation and reduced adherence to treatment [7]. Data on persistence and withdrawal rates during antimuscarinic drug therapy come almost exclusively from patients with OAB. Population-based assessments indicate that persistence rates with antimuscarinic therapy are low, even when long-acting preparations are used, and as few as 25% of patients may persist with therapy at 6 months [37-40]. Chapple et al [11] analyzed data from 56 trials and reported that patients treated with IR oxybutynin had a 40% greater risk of withdrawing from treatment than those receiving placebo. In this analysis, IR tolterodine and ER oxybutynin and tolterodine were associated with fewer withdrawals due to adverse events than IR oxybutynin.

Oxybutynin is primarily metabolized by cytochrome P450 enzyme CYP3A4. Metabolites include the pharmacologically active N-desethyloxybutynin that is thought to be the major cause of dry mouth, because it has a marginally higher affinity for muscarinic receptors in the salivary glands than the parent molecule [41]. Transdermal delivery of oxybutynin avoids presystemic first-pass metabolism, and consequently, the plasma oxybutynin:N-desethyloxybutynin ratio is more favorable than that achieved by oral delivery [27,42]. Transdermal oxybutynin has been shown to be as effective as oral therapy with an IR oral formulation [43] and long-acting oral tolterodine [44] in patients with urgency or mixed urinary incontinence. In addition, the incidence of dry mouth was markedly lower. Apart from typical antimuscarinic effects, adverse events associated with transdermal administration include application site reactions such as erythema and pruritus [43-45]. An oxybutynin topical gel formulation has been developed to reduce such application site reactions. It has demonstrated efficacy in a phase III clinical trial versus placebo, with low levels of application site pruritus (2.1%) [46]. The efficacy of transdermal oxybutynin was recently evaluated in an open-label dose-titration study in 24 patients with NDO [47]. Transdermal oxybutynin at up to 3 times the standard dose significantly increased from baseline the daily number of CIC periods without leakage, CIC volume, reflex volume, maximal cystometric bladder capacity, and residual urine volume. It also significantly decreased from baseline detrusor pressure at maximal bladder capacity. The most common adverse events were application site reactions (12.5%), dry mouth (8.3%), and blurred vision (8.3%).

Intravesical Drug Delivery

As discussed above, there is increasing awareness that the urothelium/suburothelium may play an important role in bladder activity and the coordination of detrusor muscle function [48]. Cells of the urothelium display a number of properties similar to sensory neurons. These cells can respond to various stimuli, including stretch, by releasing chemical mediators known to have excitatory or inhibitory activity on afferent neurons within or close to the urothelium, as well as direct effects on detrusor muscle contraction [49,50].

Intravesical Antimuscarinics

Muscarinic receptors are found in the urothelium at high density and play a role in modulating afferent nerves and detrusor muscle activity [51]. Intravesical administration of antimuscarinics has the potential to minimize drug levels in systemic circulation and may provide additional benefit in controlling the overactive detrusor through local inhibitory effects on muscarinic receptors in the urothelium during the bladder storage phase [52]. In adults with NDO, intravesical administration of oxybutynin was associated with restoration of continence in the majority of patients [53-55], usually with no or few systemic side effects [53-55]. Good efficacy and tolerability have also been reported after intravesical oxybutynin therapy in children with NDO [56-60]. Although the results with this approach appear promising, widespread clinical use is limited by the lack of availability of commercial solution preparations in some countries and the requirement for catheterization [52]. The antimuscarinic agent trospium chloride, a quaternary ammonium salt, does not undergo extensive metabolism; rather, 60% to 80% of the absorbed dose is excreted via the kidneys as unchanged compound, where it has the potential to exert local effects on detrusor contractility [61]. A study of patients with NDO due to spinal cord injuries demonstrated

doi:10.3834/uij.1944-5784.2009.12.10
ISSN 1944-5792 (print), ISSN 1944-5784 (online)

significant improvements in urodynamic results following 3 weeks of treatment with trospium chloride, including an increase in mean maximum cystometric capacity (MCC) and a decrease in maximum detrusor pressure [62]. Doubling the maximum recommended dosage of trospium chloride has been shown to improve urodynamic results in patients with NDO not responding to normal doses, with an acceptable tolerance profile [63].

Intravesical Vanilloids

Intravesical application of vanilloid substances such as capsaicin [64,65] and resiniferatoxin [66,67] represents another treatment alternative that has been investigated in patients with severe detrusor overactivity, including those with NDO. These agents are thought to exert their potential beneficial effects through desensitization of unmyelinated afferent C-fibers secondary to activity at the transient receptor potential cation channel V1 (TRPV1) [68]. TRPV1 receptors are also found on urothelial cells, which respond to capsaicin and other vanilloid compounds by releasing sensory transmitters, including adenosine triphosphate (ATP) [50].

In an early study, instillation of capsaicin was shown to result in significant decreases in 24-hour voiding frequency, leakages, and maximum detrusor pressure. Patients also had a significant increase in MCC compared with vehicle control [64]. A meta-analysis of studies involving patients with spinal cord injury or MS reported significant improvements in urinary incontinence episodes in patients receiving capsaicin versus placebo [69]. However, the incidence of pelvic pain or burning and flushing was significantly higher in the treatment group.

Resiniferatoxin is a potent capsaicin analogue that may induce desensitization at concentrations lower than those which cause irritation, thereby reducing the occurrence of unwanted side effects [70]. Resiniferatoxin 50 or 100 nmol/L instilled into the bladder and left for 30 minutes increased bladder volume at first detrusor contraction and MCC in patients with NDO [66]. Significant increases in bladder capacity have been documented in other studies [67,71], including one randomized controlled trial [71].

In patients refractory to antimuscarinic agents, improvements in symptoms and urodynamic parameters have been reported after resiniferatoxin therapy [72,73]. However, resiniferatoxin therapy was defined as successful in only 30% of patients with NDO, compared with 80% of patients with previous bladder outlet obstruction and 58% of those with IDO [74]. The mean duration of effect of resiniferatoxin in this study was 4.7 months (range, 3-7 months) [74]. Duration of effect in other studies has been ≥ 3 months [66] or up to 9 months [67].

Two prospective, randomized trials of patients with refractory NDO directly compared the 2 vanilloid agents. One study reported that resiniferatoxin was more effective than capsaicin for clinical and urodynamic parameters [75], whereas the second study suggested that the 2 vanilloids were equally effective and similarly tolerated [76]. Issues such as purity of agents and the nature of the delivery solvent may confound published data [76]. However, overall, the lack of a consistent reduction in detrusor pressure and reflex micturition in combination with poor tolerability has limited the use of these agents [77]. In addition, resiniferatoxin is not currently being developed because of problems with the formulation [77], and the optimum dose, concentration, and interval between instillations has not been determined for either capsaicin or resiniferatoxin [78].

Botulinum Toxin A (BoNT-A)

Recent trials have focused on injection of botulinum toxin A (BoNT-A) directly into the detrusor, and there is a good body of evidence accumulating for this treatment approach in NDO [79-81]. Botulinum toxin is the most potent naturally occurring neurotoxin known. It is produced by the gram-positive anaerobic bacteria Clostridium botulinum. Seven distinct botulinum toxins (A-G) have been identified, and subtypes A and B have been studied and used clinically. Botulinum toxin binds tightly and rapidly to nerve terminals where it cleaves specific proteins that are responsible for the docking and fusion of ACh-containing vesicles to presynaptic membranes; thus, it interfers with neurotransmitter release and results in muscle relaxation/paralysis [82]. In addition, BoNT-A has also been shown to affect sensory receptors in the urothelium, specifically the ATP-gated purinergic receptor P2X3 and/or the capsaicin receptor TRPV1, which may contribute to its overall clinical effects in the treatment of detrusor overactivity [83].

Botulinum toxin was shown to exert a prolonged local effect when injected directly into skeletal muscles, and the effects are dose-dependent and reversible. The rationale for using botulinum toxin to treat human detrusor overactivity is based on the assumption that effects of the toxin on skeletal muscle would be replicated in bladder smooth muscle [84,85] and that detrusor muscle paralysis would reduce the symptoms of bladder overactivity [86]. Botulinum toxin has been developed as a second-line treatment option (following failure of, or intolerance to, appropriate antimuscarinic therapy) for patients with NDO with urinary incontinence or other neurogenic OAB symptoms. The patients must be able and willing to perform CIC.

The first report of the application of BoNT-A in NDO appeared in 2000 [85]. Injection of BoNT-A 200–300 U at 20 to 30 detrusor

muscle sites restored continence in 17 out of 19 patients (89.5%) with severe neurogenic detrusor overactivity and incontinence secondary to traumatic spinal cord injury. Continence was observed at the 6-week follow-up. No side effects were reported. Mean reflex volume and mean maximum cystometric bladder capacity increased significantly from baseline, and there was a significant decrease in mean maximum detrusor pressure [85]. Since then, the efficacy of BoNT-A injection into the detrusor muscle in adult patients with NDO refractory to and/or intolerant of antimuscarinic agents has been confirmed in a number of studies that have been the subject of systematic review [79,80]. The analysis by Karsenty et al [80] evaluated 18 trials with onabotulinumtoxin A (BOTOX; Allergan, Inc., Irvine, CA, USA), involving a total of 698 patients; 83% of the patients had NDO with urinary incontinence. Significant benefits were seen in clinical variables (micturition frequency and number of incontinence episodes) as well as urodynamic variables (maximum detrusor pressure, MCC). Complete continence was achieved in 40% to 80% of patients [80]. Efficacy has also been demonstrated in patients with spinal cord injury and detrusor-sphincter dyssynergia [87-89]. A significant response to BoNT-A is seen as early as 1 week following treatment; however, maximum effects were seen between 1 and 4 weeks [80]. The efficacy of BoNT-A appears to persist for at least 6 months and up to 1 year. However, the benefits decline over time [90] and repeat injections are required for continued therapeutic effect. Repeat injections have been shown to be effective and well tolerated [90-92], and there is no reported evidence of a reduction in response over time after 2 to 9 repeat injections [90-92]. The beneficial clinical and urological effects of BoNT-A in adults with NDO are accompanied by improvement in patient QOL [93,94].

BoNT-A is generally well tolerated. Data from a systematic review of the role of BoNT-A in NDO indicated that the most frequent adverse events are injection site pain, procedure-related urinary tract infection, and mild hematuria [80]. A potential adverse effect resulting from the use of botulinum toxin in patients not using CIC is an increase in postvoid residual volume that may result in de novo CIC (6% to 88% of patients), with associated impact on QOL [80,95]. There have been reports of rare generalized weakness associated with use of BoNT-A to treat NDO [87,96-98].

Important factors to consider in relation to the risk of adverse events during urological use of BoNT-A are the drug dosage, formulation used, and injection technique. Available data indicate that abobotulinumtoxinA (Dysport; Ipsen Biopharm Ltd, Wrexham, UK) may be associated with a higher risk of side effects related to drug migration (eg, muscle weakness) than BOTOX [99]. It should be noted that the doses typically evaluated in clinical trials in urologic indications are not the same as the commercially available formulations of BoNT-A. It should also be noted that systemic adverse reactions, including respiratory compromise and death, have been reported following the use of BoNT-A and BoNT-B for both FDA-approved and unapproved uses [100]. The most serious cases involved treatment of children for cerebral palsy-associated limb spasticity, and the FDA is currently reviewing safety data on marketed botulinum toxin products.

Accumulating evidence indicates that BoNT-A may be a useful option for treating children with NDO and urinary incontinence and those who are refractory to antimuscarinic therapy [101]. A systematic review on the use of BoNT-A (BOTOX) in children with NDO identified 6 small (10 to 26 patients) prospective studies primarily involving children with myelomeningocele [101]. BoNT-A treatment resulted in a reduction in urinary incontinence of 40% to 80%, and between 65% and 87% of patients became completely continent between CIC. In addition, all studies showed a significant impact of treatment on urodynamic variables, including maximum detrusor pressure and MCC [101]. Improvement was observed within 2 weeks of BoNT-A injection and persisted for up to 6 months. The amount of BOTOX injected ranged from 5 to 12 U/kg, with a maximal dose of 360 U. Repeat administration of BoNT-A was associated with therapeutic effects similar to the first dose [101]. Available data therefore indicate that BoNT-A may have the ability to prevent or delay the need for surgery in children with NDO, but further studies with appropriate design and longer follow-up are required to confirm this conclusion. The safety profile in children has not been established, and there is a need for studies that evaluate the effect of long-term, repeated administration on the bladder wall.

Although the value of botulinum toxin for the treatment of NDO is now recognized in European and US consensus reports [79,81], at present the only approval for BoNT-A in a urological indication is in Brazil, where BOTOX is used for the treatment of OAB. On the whole, studies of BoNT-A are small (< 50 patients), short term, and largely restricted to patients with spinal cord injury or MS [79]. Indeed, several questions remain unanswered. These include the optimal dose and frequency of administration to balance efficacy with safety, the most appropriate method and location of administration, and how to identify patients who would benefit the most. Obviously, considerable systematic research is still required. Large phase III registration studies are being conducted to support the registration of this treatment for NDO, including the optimal dose recommendation.

doi:10.3834/uij.1944-5784.2009.12.10
ISSN 1944-5792 (print), ISSN 1944-5784 (online)

Botulinum Toxin B (BoNT-B)

There are limited data on the use of botulinum toxin type B for incontinence, particularly in patients with NDO. In the only 2 published trials on the use of BoNT-B in urologic indications, the vast majority of patients had nonneurogenic OAB [102,103]. Data on the use of BoNT-B in patients with NDO comes primarily from 3 case reports [104-106]. In one report [104], BoNT-B 5,000 U was injected into 10 different areas of the bladder wall in a patient with MS who was refractory to oral and topical antimuscarinic agents. The patient reported a positive response within 24 hours and had no adverse effects. The beneficial effects of BoNT-B began to decline after 4 months. A repeat BoNT-B dose of 7,500 U was given which also provided therapeutic benefit for 4 months. BoNT-A and BoNT-B interfere with a different presynaptic protein, meaning that a primary nonresponse to the type A toxin does not necessarily imply a nonresponse to the type B toxin. Indeed, data from the other 2 case reports indicate that BoNT-B may have a place in the management of patients with NDO resistant to therapy with the type A toxin. However, the duration of effect was only 4 to 6 weeks [105,106]. There are no data on the use of BoNT-B in children.

Electrical Stimulation

Electrical stimulation affects voltage-gated ion-canals in the neuronal conductive cell membrane. This stimulation can generate or inhibit action potentials depending on the stimulation parameters used [107]. Therapeutic options for electrical stimulation-based treatment of bladder dysfunction are activation of motor fibers in the detrusor muscle to facilitate bladder emptying and activation of the urethral closure muscles to prevent urine leakage. In addition, neuromodulation of the reflex pathways controlling lower urinary tract function can help to reestablish normal physiological function [108,109]. The exact mechanism(s) by which detrusor activity is inhibited by neuromodulation is not yet clear. The 2 main theories are: (1) direct activation of efferent fibers to the striated urethral sphincter reflexively causes detrusor relaxation; (2) somatic afferent nerve activation results in activation of inhibitory reflexes at the spinal or supraspinal level [110]. Recently, the use of positron emission tomography to measure regional cerebral blood flow during sacral neuromodulation has shown that chronic neuromodulation influences areas of the brain previously implicated in detrusor overactivity, the sense of bladder filling, and the initiation of voiding [111]. Acute sacral neuromodulation affected areas involved in sensorimotor learning, which might become less active during the course of chronic neuromodulation [111].

Neuromodulation of the sacral nerve has been used for the treatment of both storage and emptying dysfunctions, and the InterStim® device (Medtronic Inc.; Minneapolis, MN, USA) has been approved by the FDA for treatment of urgency incontinence, urgency frequency, and nonobstructive urinary retention. The lead of the implanted stimulation device is placed in the sacral S3 foramen resulting in stimulation of the sacral root S3 nerve, and implantation can be performed under local anesthesia in an outpatient setting [112]. Patients selected for sacral nerve neuromodulation undergo an initial test phase for 1 to 4 weeks to evaluate neural integrity and correct placement of leads. Generally, patients with ≥ 50% symptom improvement are eligible for a permanent device. The traditional test procedure, percutaneous nerve evaluation, is prone to lead migration and only approximately 50% of patients fulfill success criteria. Nevertheless, some patients who fail this test may still respond well after permanent implant [112]. A 2-stage implantation method was developed to improve success rates at the testing stage [113]. Further improvements have resulted in more reliable patient selection, with fewer false-negatives due to lead migration [112].

A systematic review of randomized, controlled studies evaluating sacral neuromodulation for urgency urinary incontinence revealed that approximately 80% of implanted patients achieved either continence or a ≥ 50% improvement in incontinence symptoms, compared with about 3% of control subjects receiving conservative therapy while waiting for an implant [114]. These findings were supported by the results of numerous case studies [114]. Long term follow-up (5 years) has confirmed the utility of sacral neuromodulation for urgency urinary incontinence, urinary frequency, and urinary retention [115]. Of note, there was a high degree of correlation between 1-year and 5-year success rates [115]. Surgical revision is a relatively common adverse event, occurring in up to one-third of patients [114]. Common reasons for surgical revision include relocation of the device because of pain at the implant site, lead migration, or infection [114]. New pain and undesired change in stimulation are among the frequently reported adverse effects of long-term device use [115].

In addition to the FDA-approved uses, sacral neuromodulation has been shown to be an effective treatment for urinary incontinence in adults with refractory NDO [116,117], and, in a preliminary study, in children with NDO [118]. However, these studies have had few patients [119]. Chartier-Kastler et al [117] reported the long term outcome of sacral nerve neuromodulation in 9 women (aged 26 to 53 years) with NDO refractory to conservative treatment. Five patients had MS, 2 had a spinal cord injury, and 2 had a diagnosis of myelitis. All patients had symptomatic improvements at 6 months and these remained stable for 7 of the 9 patients over a mean follow-

up period of approximately 44 months. The mean number of leaks reported per day decreased from 7.3 to 0.3 and 5 of the 9 patients were completely dry at last follow-up. Frequency was reduced from 16.1 voids/day at baseline to 8 voids/day at last follow-up. Urodynamic data at 6 months were also positive in most patients, with increases in maximum bladder capacity and volume at first contraction [117]. Interestingly, all patients reported an on-off effect that was confirmed by urodynamic measures, whereby urodynamic results at 6 months with the stimulator switched off were similar to baseline results. A recent study in patients with MS and NDO failed to document any acute effects of transcutaneous electrical stimulation of sacral dermatomes during urodynamic studies [120].

The pudendal nerve contains afferent fibers from S2 to S4 sacral nerves. Therefore, direct pudendal nerve neuromodulation will stimulate more pudendal afferents than sacral nerve stimulation and potentially avoid the side effects of mixed stimulation of the sacral root nerve (ie, stimulation of leg and buttock muscles) [110]. A variety of approaches has been tried, including development of implantable, insertable, and external pelvic floor stimulators [110]. The pudendal nerve can be accessed percutaneously within Alcock's canal. In preliminary studies, minimally invasive implanted devices have proven beneficial in treating patients with detrusor overactivity [121], including NDO [122]. The latter study involved 15 patients, including 3 with poor response to sacral neuromodulation. A significant improvement was seen in the mean number of incontinence episodes per day, and 8 patients became continent. Statistically significant improvements were also observed in urodynamic measures of MCC and maximum detrusor pressure [122]. The Bion® device (Boston Scientific; Natick, MA, USA) is a self-contained, telemetrically programmable neurostimulatory device currently undergoing clinical evaluation in the United States and Europe. Interestingly, studies comparing sacral and pudendal nerve stimulation have indicated greater effects of pudendal nerve stimulation on voiding parameters in patients with voiding dysfunction [123] or interstitial cystitis [124].

A terminal, superficial branch of the pudendal nerve is the dorsal genital nerve that carries sensory information from the glans of the penis or clitoris. Transcutaneous electrical stimulation of this nerve with surface electrodes has shown potential in treating NDO in patients with spinal cord injuries [125,126]. In 2 studies, the majority of patients had at least 1 inhibited detrusor contraction and increased bladder capacity as a result of continuous or conditional (based on intravesical pressure) stimulation.

The posterior tibial nerve is a mixed sensory and motor nerve containing fibers from spinal roots L4 to S3, which modulate the somatic and autonomic nerves to the bladder and urinary sphincter as well as to the pelvic floor [110]. Stimulation of the posterior tibial nerve to inhibit detrusor overactivity has been shown to produce improvements in subjective and objective parameters in patients with OAB following 12 weeks of treatment [127] and to have an acute effect on urodynamic parameters in patients with NDO due to MS, PD, or spinal cord injury [128,129]. In the latter studies, posterior tibial nerve stimulation resulted in a significant increase in mean first involuntary detrusor contraction volume and MCC [128,129].

The beneficial effects of electrical stimulation only occur during the period of stimulation; there is no persistent benefit of treatment once electrical stimulation is stopped. In addition, the characteristics of NDO can change over time and with comorbid disease progression. Therefore, repeat urodynamic assessment may be necessary when symptoms recur during therapy that was previously effective [110].

CONCLUSIONS

There is an expanding range of treatment options available for the patient presenting with NDO. First-line therapy consists of oral antimuscarinic agents, although many patients will experience treatment-limiting adverse events. Alternative approaches include transdermal or intravesical administration of antimuscarinics, intravesical administration of other agents (including vanilloids and BoNT-A), and electrical stimulation. The available alternatives have demonstrated varying degrees of efficacy and all are minimally invasive, allowing surgery to be avoided where possible. Treatment should always begin with the most reversible forms of therapy and progress to more complex options. This process is facilitated by the availability of a variety of minimally invasive therapies for the management of NDO. In addition, it is important to choose a therapy that considers the needs of individual patients.

ACKNOWLEDGEMENTS

Editorial assistance for the preparation of this manuscript was provided by Nicola Ryan, Rod McNab, and Sushma Soni. This assistance was funded by Allergan, Inc.

Conflict of Interest:

Karl-Erik Andersson is a paid consultant to Allergan Inc, Astellas Pharma US Inc, ONO Pharmaceutical Co Ltd, Novartis Pharmaceuticals Corp, and Pfizer Inc.

Roger Dmochowski is a paid consultant to Allergan Inc.

Alan Wein is a paid consultant to Astellas Pharma US Inc, Novartis Pharmaceuticals Corp, and Pfizer Inc.

doi:10.3834/uij.1944-5784.2009.12.10
ISSN 1944-5792 (print), ISSN 1944-5784 (online)

REFERENCES

[1] Fowler CJ, Griffiths D, de Groat WC. The neural control of micturition. *Nat Rev Neurosci*. 2008 Jun;9(6):453-466.

[2] Kaplan SA, Chancellor MB, Blaivas JG. Bladder and sphincter behavior in patients with spinal cord lesions. *J Urol*. 1991;146(1):113-117.

[3] Smith DB. Urinary incontinence and diabetes: a review. *J Wound Ostomy Continence Nurs*. 2006;33(6):619-623.

[4] Wein AJ. Lower urinary tract dysfunction in neurologic injury and disease. In: Wein AJ, Kavoussi LR, Novick AC, et al., eds. *Campbell-Walsh Urology*. 9th ed. Philadelphia, PA: Saunders; 2007:2011-2045.

[5] Garcia Leoni ME, Esclarin De Ruz A. Management of urinary tract infection in patients with spinal cord injuries. *Clin Microbiol Infect*. 2003;9(8):780-785.

[6] Jackson S. The patient with an overactive bladder—symptoms and quality-of-life issues. *Urology*. 1997;50(6A suppl):18-24.

[7] Denys P, Corcos J, Everaert K, et al. Improving the global management of the neurogenic bladder patient: part II. Future treatment strategies. *Curr Med Res Opin*. 2006;22(5):851-860.

[8] Hashim H, Abrams P. Is the bladder a reliable witness for predicting detrusor overactivity? *J Urol*. 2006;175(1):191-195.

[9] Chancellor MB, Anderson RU, Boone TB. Pharmacotherapy for neurogenic detrusor overactivity. *Am J Phys Med Rehabil*. 2006;85(6):536-545.

[10] Abrams P, Andersson KE. Muscarinic receptor antagonists for overactive bladder. *BJU Int*. 2007;100(5):987-1006.

[11] Chapple C, Khullar V, Gabriel Z, Dooley JA. The effects of antimuscarinic treatments in overactive bladder: a systematic review and meta-analysis. *Eur Urol*. 2005;48(1):5-26.

[12] Hegde SS, Choppin A, Bonhaus D, et al. Functional role of M2 and M3 muscarinic receptors in the urinary bladder of rats in vitro and in vivo. *Br J Pharmacol*. 1997;120(8):1409-1418.

[13] Ehlert FJ, Griffin MT, Abe DM, et al. The M2 muscarinic receptor mediates contraction through indirect mechanisms in mouse urinary bladder. *J Pharmacol Exp Ther.* 2005;313(1):368-378.

[14] Mukerji G, Yiangou Y, Grogono J, et al. Localization of M2 and M3 muscarinic receptors in human bladder disorders and their clinical correlations. *J Urol*. 2006;176(1):367-373.

[15] Andersson KE. Bladder activation: afferent mechanisms. *Urology*. 2002;59(suppl 1):43-50.

[16] Andersson KE. Antimuscarinics for treatment of overactive bladder. *Lancet Neurol*. 2004;3(1):46-53.

[17] Andersson KE, Yoshida M. Antimuscarinics and the overactive detrusor—which is the main mechanism of action? *Eur Urol*. 2003;43(1):1-5.

[18] Yarker YE, Goa KL, Fitton A. Oxybutynin. A review of its pharmacodynamic and pharmacokinetic properties, and its therapeutic use in detrusor instability. *Drugs Aging.* 1995;6(3):243-262.

[19] Nabi G, Cody DJ, Ellis G, Herbison P, Hay-Smith EJC,. Anticholinergic drugs versus placebo for overactive bladder syndrome in adults. Grant AM, Glazener CM, Cody DJ, Walker SA, eds. *Cochrane Database Syst Rev*. 2006, Issue 4. Art. No.: CD003781. DOI: 10.1002/14651858.CD003781.pub2. http://www.abdn.ac.uk/hsru/publications/cochrane/. Accessed November 4, 2009.

[20] Chapple CR, Khullar V, Gabriel Z, Muston D, Bitoun CE, Weinstein D. The effects of antimuscarinic treatments in overactive bladder: an update of a systematic review and meta-analysis. *Eur Urol*. 2008;54(3):543-562.

[21] Khullar V, Chapple C, Gabriel Z, Dooley JA. The effects of antimuscarinics on health-related quality of life in overactive bladder: a systematic review and meta-analysis. *Urology*. 2006;68(suppl 2):38-48.

[22] Alhasso A, McKinlay A, Patrick K, Stewart L. Anticholinergic drugs versus non-drug active therapies for overactive bladder syndrome in adults. Grant AM, Glazener CM, Cody DJ, Walker SA, eds. *Cochrane Database Syst Rev*. 2006, Issue 4. Art. No.: CD003193. DOI: 10.1002/14651858.CD003193.pub3. http://www.abdn.ac.uk/hsru/publications/cochrane/. Accessed November 4, 2009.

[23] Abrams P, Andersson KE, Buccafusco JJ, et al. Muscarinic receptors: their distribution and function in body systems, and the implications for treating overactive bladder. *Br J Pharmacol*. 2006;148(5):565-578.

[24] Novartis Pharmaceuticals Corp. ENABLEX (darifenacin) extended release tablets: prescribing information (revised June 2008). http://www.pharma.us.novartis.com/product/pi/pdf/enablex.pdf. Accessed November 4, 2009.

[25] Pfizer Inc. Toviaz (fesoterodine fumarate) extended-release tablets: prescribing information (revised November 2008). http://media.pfizer.com/files/products/uspi_toviaz.pdf. Accessed November 4, 2009.

[26] Ortho-McNeil, Janssen Pharmaceuticals. DITROPAN XL (oxybutynin chloride) extended release tablets: prescribing information (revised February 2008). http://www.ortho-mcneilpharmaceutical.com/ortho-mcneilpharmaceutical/shared/pi/ditropanxl.pdf#zoom=100. Accessed November 4, 2009.

[27] Watson Pharmaceuticals Inc. OXYTROL (oxybutynin transdermal system) patch: prescribing information (revised May 2006). http://pi.watson.com/data_stream.asp?product_group=1295&p=pi&language=E. Accessed November 4, 2009.

[28] Watson Pharmaceuticals Inc. GELNIQUE (oxybutynin chloride) 10% gel: prescribing information (revised January 2009). http://pi.watson.com/data_stream.asp?product_group=1634&p=pi&language=E. Accessed November 4, 2009.

[29] Astellas Pharma US, Inc. and GlaxoSmithKline. VESIcare (solifenacin succinate) tablets: prescribing information (revised November 2008). http://www.astellas.us/docs/vesicare.pdf. Accessed November 4, 2009.

[30] Pfizer Inc. Detrol LA (tolterodine tartrate) extended release capsules: prescribing information (revised March 2008). http://media.pfizer.com/files/products/uspi_detrol_la.pdf. Accessed November 4, 2009.

[31] Allergan, Inc. SANCTURA XR (trospium chloride extended release): prescribing information (revised November 2008). http://www.allergan.com/assets/pdf/sanctura_xr_pi.pdf. Accessed November 4, 2009.

[32] Roden DM. Drug-induced prolongation of the QT interval. *N Engl J Med*. 2004;350(10):1013-1022.

[33] Andersson KE, Olshansky B. Treating patients with overactive bladder syndrome with antimuscarinics: heart rate considerations. *BJU Int*. 2007;100(5):1007-1014.

[34] Farrall AJ, Wardlaw JM. Blood-brain barrier: Ageing and microvascular disease - systematic review and meta-analysis. *Neurobiol Aging*. 2009;30(3):337-352.

[35] Kay GG, Abou-Donia MB, Messer WS Jr, Murphy DG, Tsao JW, Ouslander JG. Antimuscarinic drugs for overactive bladder and their potential effects on cognitive function in older patients. *J Am Geriatr Soc*. 2005;53(12):2195-2201.

[36] Edwards KR, O'Connor JT. Risk of delirium with concomitant use of tolterodine and acetylcholinesterase inhibitors. *J Am Geriatr Soc*. 2002;50(6):1165-1166.

[37] Lawrence M, Guay DR, Benson SR, Anderson MJ. Immediate-release oxybutynin versus tolterodine in detrusor overactivity: a population analysis. *Pharmacotherapy.* 2000;20(4):470-475.

[38] Shaya FT, Blume S, Gu A, Zyczynski T, Jumadilova Z. Persistence with overactive bladder pharmacotherapy in a Medicaid population. *Am J Manag Care*. 2005;11(4 suppl):S121-S129.

[39] Varadharajan S, Jumadilova Z, Girase P, Ollendorf DA. Economic impact of extended-release tolterodine versus immediate- and extended-release oxybutynin among commercially insured persons with overactive bladder. *Am J Manag Care*. 2005;11(4 suppl):S140-S149.

[40] Perfetto EM, Subedi P, Jumadilova Z. Treatment of overactive bladder: a model comparing extended-release formulations of tolterodine and oxybutynin. *Am J Manag Care*. 2005;11(4 suppl):S150-S157.

[41] Waldeck K, Larsson B, Andersson KE. Comparison of oxybutynin and its active metabolite, N-desethyl-oxybutynin, in the human detrusor and parotid gland. *J Urol.* 1997;157(3):1093-1097.

[42] Shaw GL, Patel HR. Transdermal oxybutynin: a review. *Expert Opin Drug Metab Toxicol*. 2007;3(3):435-439.

[43] Davila GW, Daugherty CA, Sanders SW. A short-term, multicenter, randomized double-blind dose titration study of the efficacy and anticholinergic side effects of transdermal compared to immediate release oral oxybutynin treatment of patients with urge urinary incontinence. *J Urol.* 2001;166(1):140-145.

[44] Dmochowski RR, Sand PK, Zinner NR, et al. Comparative efficacy and safety of transdermal oxybutynin and oral tolterodine versus placebo in previously treated patients with urge and mixed urinary incontinence. *Urology.* 2003;62(2):237-242.

[45] Dmochowski RR, Davila GW, Zinner NR, et al. Efficacy and safety of transdermal oxybutynin in patients with urge and mixed urinary incontinence. *J Urol*. 2002;168(2):580-586.

[46] Staskin DR, Dmochowski RR, Sand PK, et al. Efficacy and safety of oxybutynin chloride topical gel for overactive bladder: a randomized, double-blind, placebo controlled, multicenter study. *J Urol*. 2009;181(4):1764-1772.

[47] Kennelly MJ, Lemack GE, Foote JE, Trop CS. Efficacy and safety of oxybutynin transdermal system in spinal cord injury patients with neurogenic detrusor overactivity and incontinence: an open-label, dose-titration study. *Urology*. 2009;74(4):741-745.

[48] Birder LA, de Groat WC. Mechanisms of disease: involvement of the urothelium in bladder dysfunction. *Nat Clin Pract Urol*. 2007;4(1):46-54.

[49] Birder LA. Role of the urothelium in urinary bladder dysfunction following spinal cord injury. *Prog Brain Res*. 2006;152:135-146

[50] de Groat WC. The urothelium in overactive bladder: passive bystander or active participant? *Urology*. 2004;64(6 suppl 1):7-11.

[51] Masuda H, Kim YT, Tyagi S, Chancellor MB, de Miguel F, Yoshimura N. Local effects of antimuscarinics. *Urol Clin North Am*. 2006;33(40:511-518.

[52] Reitz A, Schurch B. Intravesical therapy options for neurogenic detrusor overactivity. *Spinal Cord*. 2004;42(5):267-272.

[53] Brendler CB, Radebaugh LC, Mohler JL. Topical oxybutynin chloride for relaxation of dysfunctional bladders. *J Urol*. 1989;141(6):1350-1352.

[54] Madersbacher H, Jilg G. Control of detrusor hyperreflexia by the intravesical instillation of oxybutynine hydrochloride. *Paraplegia*. 1991;29(2):84-90.

[55] Massad CA, Kogan BA, Trigo-Rocha FE. The pharmacokinetics of intravesical and oral oxybutynin chloride. *J Urol*. 1992;148(2 Pt 2):595-597.

[56] Buyse G, Verpoorten C, Vereecken R, Casaer P. Intravesical application of a stable oxybutynin solution improves therapeutic compliance and acceptance in children with neurogenic bladder dysfunction. *J Urol*. 1998;160(3 Pt 2):1084-1092.

[57] Amark P, Bussman G, Eksborg S. Follow-up of long-time treatment with intravesical oxybutynin for neurogenic bladder in children. *Eur Urol*. 1998;34(2):148-153.

[58] Amark P, Eksborg S, Juneskans O, Bussman G, Palm C. Pharmacokinetics and effects of intravesical oxybutynin on the paediatric neurogenic bladder. *Br J Urol*. 1998;82:859-864.

[59] Kasabian NG, Vlachiotis JD, Lais A, et al. The use of intravesical oxybutynin chloride in patients with detrusor hypertonicity and detrusor hyperreflexia. *J Urol.* 1994;151(4):944-945.

[60] Palmer LS, Zebold K, Firlit CF, Kaplan WE. Complications of intravesical oxybutynin chloride therapy in the pediatric myelomeningocele population. *J Urol*. 1997;157(2):638-640.

[61] Kim Y, Yoshimura N, Masuda H, De Miguel F, Chancellor MB. Intravesical instillation of human urine after oral administration of trospium, tolterodine and oxybutynin in a rat model of detrusor overactivity. *BJU Int*. 2006;97(2):400-403.

[62] Stohrer M, Bauer P, Giannetti BM, Richter R, Burgdorfer H, Murtz G. Effect of trospium chloride on urodynamic parameters in patients with detrusor hyperreflexia due to spinal cord injuries. A multicentre placebo-controlled double-blind trial. *Urol Int*. 1991;47(3):138-143.

[63] Horstmann M, Schaefer T, Aguilar Y, Stenzl A, Sievert KD. Neurogenic bladder treatment by doubling the recommended antimuscarinic dosage. *Neurourol Urodyn*. 2006;25(5):441-445.

[64] de Seze M, Wiart L, Joseph PA, Dosque JP, Mazaux JM, Barat M. Capsaicin and neurogenic detrusor hyperreflexia: a double-blind placebo-controlled study in 20 patients with spinal cord lesions. *Neurourol Urodyn*. 1998;17(5):513-523.

[65] Fowler CJ, Jewkes D, McDonald WI, Lynn B, de Groat WC. Intravesical capsaicin for neurogenic bladder dysfunction. *Lancet*. 1992;339(8803):1239.

[66] Cruz F, Guimaraes M, Silva C, Reis M. Suppression of bladder hyperreflexia by intravesical resiniferatoxin. *Lancet*. 1997;350(9078):640-641.

[67] Watanabe T, Yokoyama T, Sasaki K, Nozaki K, Ozawa H, Kumon H. Intravesical resiniferatoxin for patients with neurogenic detrusor overactivity. *Int J Urol*. 2004;11(4):200-205.

[68] Fowler CJ. Intravesical treatment of overactive bladder. *Urology*. 2000;55(5A suppl):60-66.

[69] MacDonald R, Monga M, Fink HA, Wilt TJ. Neurotoxin treatments for urinary incontinence in subjects with spinal cord injury or multiple sclerosis: a systematic review of effectiveness and adverse effects. *J Spinal Cord Med*. 2008;31(2):157-165.

[70] Szallasi A, Blumberg PM. Vanilloid receptors: new insights enhance potential as a therapeutic target. *Pain*. 1996;68(2-3):195-208.

[71] Silva C, Silva J, Ribeiro MJ, Avelino A, Cruz F. Urodynamic effect of intravesical resiniferatoxin in patients with neurogenic detrusor overactivity of spinal origin: results of a double-blind randomized placebo-controlled trial. *Eur Urol*. 2005;48(4):650-655.

[72] Lazzeri M, Spinelli M, Zanollo A, Turini D. Intravesical vanilloids and neurogenic incontinence: ten years experience. *Urol Int*. 2004;72(2):145-149.

[73] Kim JH, Rivas DA, Shenot PJ, et al. Intravesical resiniferatoxin for refractory detrusor hyperreflexia: a multicenter, blinded, randomized, placebo-controlled trial. *J Spinal Cord Med*. 2003;26(4):358-363.

[74] Kuo HC. Multiple intravesical instillation of low-dose resiniferatoxin is effective in the treatment of detrusor overactivity refractory to anticholinergics. *BJU Int*. 2005;95(7):1023-1027.

[75] Giannantoni A, Di Stasi SM, Stephen RL, et al. Intravesical capsaicin versus resiniferatoxin in patients with detrusor hyperreflexia: a prospective randomized study. *J Urol.* 2002;167(4):1710-1714.

[76] de Seze M, Wiart L, de Seze MP, et al. Intravesical capsaicin versus resiniferatoxin for the treatment of detrusor hyperreflexia in spinal cord injured patients: a double-blind, randomized, controlled study. *J Urol*. 2004;171(1):251-255.

[77] Andersson KE, Appell RA, Cardozo L, et al. Pharmacological treatment of urinary incontinence In: Abrams C, Khoury S, Wein A, eds. *International Consultation on Incontinence*. 2005 ed. Paris: Health Publications; 2005:809-854.

[78] Nitti VW, Blaivas JG. Urinary incontinence: epidemiology, pathophysiology, evaluation and management. In: Wein AJ, Kavoussi LR, Novick AC, et al, eds. *Campbell-Walsh Urology.* 9th ed. Philadelphia, PA: Saunders; 2007:2046-2078.

[79] Apostolidis A, Dasgupta P, Denys P, et al. Recommendations on the use of botulinum toxin in the treatment of lower urinary tract disorders and pelvic floor dysfunctions: a European consensus report. *Eur Urol*. 2009;55(1):100-120.

[80] Karsenty G, Denys P, Amarenco G, et al. Botulinum toxin A (BOTOX) intradetrusor injections in adults with neurogenic detrusor overactivity/neurogenic overactive bladder: a systematic literature review. *Eur Urol*. 2008;53(2):275-287.

[81] Naumann M, So Y, Argoff CE, et al. Assessment: Botulinum neurotoxin in the treatment of autonomic disorders and pain (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2008;70(19):1707-1714.

[82] Nitti VW. Botulinum toxin for the treatment of idiopathic and neurogenic overactive bladder: state of the art. *Rev Urol.* 2006;8(4):198-208.

[83] 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):977-983.

[84] Schurch B, Schmid DM, Stohrer M. Treatment of neurogenic incontinence with botulinum toxin A. *N Engl J Med*. 2000;342(9):665.

[85] Schurch B, Stohrer M, Kramer G, Schmid DM, Gaul G, Hauri D. Botulinum-A toxin for treating detrusor hyperreflexia in spinal cord injured patients: a new alternative to anticholinergic drugs? Preliminary results. *J Urol.* 2000;164(3 Pt 1):692-697.

[86] Duthie J, Wilson DI, Herbison GP, Wilson D. Botulinum toxin injections for adults with overactive bladder syndrome. *Cochrane Database Syst Rev.* 2007, Issue 3. Art. No.: CD005493. DOI: 10.1002/14651858.CD005493.pub2. http://www.abdn.ac.uk/hsru/publications/cochrane/. Accessed November 4, 2009.

[87] Dykstra DD, Sidi AA. Treatment of detrusor-sphincter dyssynergia with botulinum A toxin: a double-blind study. *Arch Phys Med Rehabil*. 1990;71(1):24-26.

[88] Schurch B, Hauri D, Rodic B, Curt A, Meyer M, Rossier AB. Botulinum-A toxin as a treatment of detrusor-sphincter dyssynergia: a prospective study in 24 spinal cord injury patients. *J Urol*. 1996;155(3):1023-1029.

[89] Schurch B, Schmid DM, Knapp PA. An update on the treatment of detrusor-sphincter dyssynergia with botulinum toxin type A. *Eur J Urol*. 1999;6(suppl. 4):S83-S89.

[90] Grosse J, Kramer G, Stohrer M. Success of repeat detrusor injections of botulinum a toxin in patients with severe neurogenic detrusor overactivity and incontinence. *Eur Urol*. 2005;47(5):653-659.

[91] Giannantoni A, Mearini E, Del Zingaro M, Porena M. Six-year follow-up of botulinum toxin A intradetrusorial injections in patients with refractory neurogenic detrusor overactivity: clinical and urodynamic results. *Eur Urol.* 2009;55(3):705-711.

[92] Karsenty G, Reitz A, Lindemann G, Boy S, Schurch B. Persistence of therapeutic effect after repeated injections of botulinum toxin type A to treat incontinence due to neurogenic detrusor overactivity. *Urology*. 2006;68(6):1193-1197.

[93] Kalsi V, Apostolidis A, Popat R, Gonzales G, Fowler CJ, Dasgupta P. Quality of life changes in patients with neurogenic versus idiopathic detrusor overactivity after intradetrusor injections of botulinum neurotoxin type A and correlations with lower urinary tract symptoms and urodynamic changes. *Eur Urol*. 2006;49(3):528-535.

[94] 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.

[95] Shaban AM, Drake MJ. Botulinum toxin treatment for overactive bladder: risk of urinary retention. *Curr Urol Rep*. 2008;9(6):445-451.

[96] Akbar M, Abel R, Seyler TM, et al. Repeated botulinum-A toxin injections in the treatment of myelodysplastic children and patients with spinal cord injuries with neurogenic bladder dysfunction. *BJU Int.* 2007;100(3):639-645.

[97] Ruffion A, Capelle O, Paparel P, Leriche B, Leriche A, Grise P. What is the optimum dose of type A botulinum toxin for treating neurogenic bladder overactivity? *BJU Int*. 2006;97(5):1030-1034.

[98] 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.

[99] Dmochowski R, Sand PK. Botulinum toxin A in the overactive bladder: current status and future directions. *BJU Int*. 2007;99(2):247-262.

[100] US Food and Drug Administration, Center for Drug Evaluation and Research. Early communication about an ongoing safety review: Botox and Botox Cosmetic (botulinum toxin type A) and Myobloc (botulinum toxin type B). Vol 2009. FDA Web site. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm070366.htm. Accessed November 4, 2009.

[101] Game X, Mouracade P, Chartier-Kastler E, et al. Botulinum toxin-A (Botox) intradetrusor injections in children with neurogenic detrusor overactivity/neurogenic overactive bladder: a systematic literature review. *J Pediatr Urol*. 2009;5(3):156-164.

[102] Dykstra D, Enriquez A, Valley M. Treatment of overactive bladder with botulinum toxin type B: a pilot study. *Int Urogynecol J Pelvic Floor Dysfunct*. 2003;14(6):424-426.

[103] Ghei M, Maraj BH, Miller R, et al. Effects of botulinum toxin B on refractory detrusor overactivity: a randomized, double-blind, placebo controlled, crossover trial. *J Urol.* 2005;174(5):1873-1877.

[104] Dykstra DD, Pryor J, Goldish G. Use of botulinum toxin type B for the treatment of detrusor hyperreflexia in a patient with multiple sclerosis: a case report. *Arch Phys Med Rehabil*. 2003;84(9):1399-1400.

[105] 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.

[106] Reitz A, Schurch B. Botulinum toxin type B injection for management of type A resistant neurogenic detrusor overactivity. *J Urol*. 2004;171(2 Pt 1):804-805.

[107] Dalmose A, Bjarkam C, Vuckovic A, Sorensen JC, Hansen J. Electrostimulation: a future treatment option for patients with neurogenic urodynamic disorders? *APMIS Suppl*. 2003;109:45-51.

[108] Jezernik S, Craggs M, Grill WM, Creasey G, Rijkhoff NJ. Electrical stimulation for the treatment of bladder dysfunction: current status and future possibilities. *Neurol Res*. 2002;24(5):413-430.

[109] Rijkhoff NJ. Neuroprostheses to treat neurogenic bladder dysfunction: current status and future perspectives. *Childs Nerv Syst*. 2004;20(2):75-86.

[110] Vasavada SP, Rackley RR. Electrical stimulation for storage and emptying disorders. In: Wein AJ, Kavoussi LR, Novick AC, et al., eds. *Campbell-Walsh Urology.* 9th ed. Philadelphia, PA: Saunders; 2007:2147-2167.

[111] Blok BF, Groen J, Bosch JL, Veltman DJ, Lammertsma AA. Different brain effects during chronic and acute sacral neuromodulation in urge incontinent patients with implanted neurostimulators. *BJU Int*. 2006;98(6):1238-1243.

[112] Chartier-Kastler E. Sacral neuromodulation for treating the symptoms of overactive bladder syndrome and non-obstructive urinary retention: >10 years of clinical experience. *BJU Int*. 2008;101(4):417-423.

[113] Janknegt RA, Weil EH, Eerdmans PH. Improving neuromodulation technique for refractory voiding dysfunctions: two-stage implant. *Urology*. 1997;49(3):358-362.

[114] Brazzelli M, Murray A, Fraser C. Efficacy and safety of sacral nerve stimulation for urinary urge incontinence: a systematic review. *J Urol.* 2006;175(3 Pt 1):835-841.

[115]van Kerrebroeck PE, van Voskuilen AC, Heesakkers JP, et al. Results of sacral neuromodulation therapy for urinary voiding dysfunction: outcomes of a prospective, worldwide clinical study. *J Urol*. 2007;178(5):2029-2034.

[116]Bosch JL, Groen J. Neuromodulation: urodynamic effects of sacral (S3) spinal nerve stimulation in patients with detrusor instability or detrusor hyperflexia. *Behav Brain Res*. 1998;92(2):141-150.

[117]Chartier-Kastler EJ, Ruud Bosch JL, Perrigot M, Chancellor MB, Richard F, Denys P. Long-term results of sacral nerve stimulation (S3) for the treatment of neurogenic refractory urge incontinence related to detrusor hyperreflexia. *J Urol*. 2000;164(5):1476-1480.

[118] Guys JM, Haddad M, Planche D, Torre M, Louis-Borrione C, Breaud J. Sacral neuromodulation for neurogenic bladder dysfunction in children. *J Urol*. 2004;172(4 Pt 2):1673-1676.

[119] Hohenfellner M, Humke J, Hampel C, et al. Chronic sacral neuromodulation for treatment of neurogenic bladder dysfunction: long-term results with unilateral implants. *Urology*. 2001;58(6):887-892.

[120] Fjorback MV, Van Rey FS, Rijkhoff NJ, Nohr M, Petersen T, Heesakkers JP. Electrical stimulation of sacral dermatomes in multiple sclerosis patients with neurogenic detrusor overactivity. *Neurourol Urodyn*. 2007;26(4):525-530.

[121] Bosch JL. The bion device: a minimally invasive implantable ministimulator for pudendal nerve neuromodulation in patients with detrusor overactivity incontinence. *Urol Clin North Am*. 2005;32(1):109-112.

[122] Spinelli M, Malaguti S, Giardiello G, Lazzeri M, Tarantola J, Van Den Hombergh U. A new minimally invasive procedure for pudendal nerve stimulation to treat neurogenic bladder: description of the method and preliminary data. *Neurourol Urodyn*. 2005;24(4):305-309.

[123] Peters KM, Feber KM, Bennett RC. Sacral versus pudendal nerve stimulation for voiding dysfunction: a prospective, single-blinded, randomized, crossover trial. *Neurourol Urodyn*. 2005;24(7):643-647.

[124] Peters KM, Feber KM, Bennett RC. A prospective, single-blind, randomized crossover trial of sacral vs pudendal nerve stimulation for interstitial cystitis. *BJU Int*. 2007;100(4):835-839.

[125] Hansen J, Media S, Nohr M, Biering-Sorensen F, Sinkjaer T, Rijkhoff NJ. Treatment of neurogenic detrusor overactivity in spinal cord injured patients by conditional electrical stimulation. *J Urol*. 2005;173(6):2035-2039.

[126] Kirkham AP, Shah NC, Knight SL, Shah PJ, Craggs MD. The acute effects of continuous and conditional neuromodulation on the bladder in spinal cord injury. *Spinal Cord*. 2001;39(8):420-428.

[127] Vandoninck V, Van Balken MR, Finazzi Agro E, et al. Posterior tibial nerve stimulation in the treatment of urge incontinence. *Neurourol Urodyn*. 2003;22(1):17-23.

[128] Kabay SC, Yucel M, Kabay S. Acute effect of posterior tibial nerve stimulation on neurogenic detrusor overactivity in patients with multiple sclerosis: urodynamic study. *Urology.* 2008;71(4):641-645.

[129] Amarenco G, Ismael SS, Even-Schneider A, et al. Urodynamic effect of acute transcutaneous posterior tibial nerve stimulation in overactive bladder. *J Urol.* 2003;169(6):2210-2215.

doi:10.3834/uij.1944-5784.2009.12.10
ISSN 1944-5792 (print), ISSN 1944-5784 (online)