Experience with botulinum toxin type A in the treatment of neurogenic detrusor overactivity in clinical practice

Ther Adv Urol

2014, Vol 6(1) 34–42

DOI: 10.1177/1756287213510962

Stephanie Knuepfer and Klaus-Peter Juenemann

Abstract: Control of the lower urinary tract is a complex, multilevel process that involves both the peripheral and central nervous system. Neurogenic lower urinary tract dysfunction (LUTD) is a widespread chronic illness that impairs millions of people worldwide. Neurogenic LUTD has a major impact on quality of life, affecting emotional, social, sexual, occupational and physical aspects of daily life, and in addition to the debilitating manifestations for patients, it also imposes a substantial economic burden on every healthcare system. First-line treatment for neurogenic LUTD includes antimuscarinics and some form of catheterization, preferably intermittent self-catheterization. However, the treatment effect is often unsatisfactory, so that other options have to be considered. Moreover, neurogenic LUTD is a challenge because all available treatment modalities (i.e. conservative, minimally invasive and invasive therapies) may fail. In recent years, botulinum neurotoxin type A (BoNT/A) treatment has been shown to be an effective pharmacological therapy option in patients refractory to antimuscarinic and neurogenic detrusor overactivity (NDO). Several studies have shown that BoNT/A injection significantly reduces detrusor muscle overactivity. Also BoNT/A treatment of NDO has revealed a significant improvement of lower urinary tract function with regard to reduced urinary incontinence, reduced detrusor pressure, increased bladder capacity and improved quality of life in NDO.

Keywords: botulinum toxin injection, neurogenic bladder dysfunction, overactive bladder, urinary bladder

Introduction

Control of the lower urinary tract is a complex, multilevel process that involves both the peripheral and central nervous system [Fowler *et al.* 2008]. Neurogenic lower urinary tract dysfunction (LUTD) is a widespread chronic illness that impairs millions of people worldwide. Neurogenic LUTD has a major impact on quality of life, affecting emotional, social, sexual, occupational and physical aspects of daily life, and in addition to the debilitating manifestations for patients, it also imposes a substantial economic burden on every healthcare system. First-line treatment for neurogenic LUTD includes antimuscarinics and some form of catheterization, preferably intermittent self-catheterization. However, the treatment effect is often unsatisfactory, so that other options have to be considered. Moreover, neurogenic LUTD is a challenge because all available treatment modalities (i.e. conservative, minimally invasive and invasive therapies) may fail.

In recent years, botulinum neurotoxin type A (BoNT/A) treatment has been identified as an effective pharmacological therapy option in patients refractory to antimuscarinic and neurogenic detrusor overactivity (NDO). Several studies have shown significantly reduced detrusor muscle overactivity following BoNT/A injection. Also BoNT/A treatment of NDO reveals a significant improvement of lower urinary tract function with regard to reduced urinary incontinence (UI), reduced detrusor pressure, increased bladder capacity and improved quality of life in NDO [Apostolidis *et al.* 2009; Karsenty *et al.* 2008]. However, modulation of neuromuscular

Correspondence to:
Stephanie Knuepfer, MD
Spinal Cord Injury Center & Research, University Zürich, Balgrist University Hospital, Zürich, Forchstrasse 340, 8008 CH, Switzerland
sknuepfer@paralab.balgrist.ch

Klaus-Peter Juenemann, MD
University of Kiel, Kiel, Germany University Hospital of Urology Germany

transmission may also result in urinary retention, and for this reason BoNT/A treatment is still under debate. In 2000, Schurch and colleagues first published on the use of botulinum toxin injections into the detrusor for the treatment of NDO in patients with spinal cord injury (SCI) [Schurch *et al*. 2000a, 2000b]. Since then, intradetrusor BoNT/A injections have become a well-established and widely accepted therapy for refractory neurogenic and non-neurogenic overactive bladder (OAB) with or without urodynamically proven detrusor overactivity (DO) [Apostolidis *et al.* 2009; Mangera *et al.* 2011]. Although BoNT/A injection into the detrusor is a highly effective, minimally invasive and generally well-tolerated treatment that improves quality of life, the use of BoNT/A in the lower urinary tract is still not licensed in several countries.

Definition of detrusor overactivity

The International Continence Society (ICS) formally defined OAB in September 2001 as a 'symptom syndrome of lower urinary tract dysfunction'. More specifically, OAB is defined as 'urgency, with or without urge incontinence, usually with frequency and nocturia' [Abrams *et al.* 2002]. Synonyms include urge syndrome and urgency–frequency syndrome. When there is a relevant underlying neurological condition [e.g. SCI or multiple sclerosis (MS)], this is qualified as NDO [Abrams *et al.* 2002]. Patients with certain conditions such as Parkinson's disease, stroke and dementia are at risk for bladder dysfunction. Around 20–30% of patients with Parkinson's and MS present with bladder dysfunction before diagnosis of the disease. The overall incidence of bladder dysfunction ranges from 40% to 70% in Parkinson's disease [Karram, 1999].

Owing to the complexity of neural bladder control, the interconnection is sensitive to various diseases and injuries. Changes in central and peripheral neurologic pathways that may result in OAB include: (1) a decrease in central or peripheral inhibition; (2) an increase in excitatory reflex pathways; (3) increased afferent input from the lower urinary tract; and (4) development of bladder reflexes resistant to central inhibition [deGroat, 1997].

In the last few years, several studies have proposed that the afferent nervous system plays an important role in the regulation of lower urinary tract function. In addition to being active during the storage phase, afferent nerves are closely involved in the micturition reflex; some research suggests that afferents may provide a positive feedback mechanism during voiding, ensuring complete bladder emptying [Kruse *et al.* 1991].

The involuntary contractile activity of detrusor smooth muscle during filling may generate afferent input and in pathological conditions, e.g. OAB/DO, may contribute to these disorders [Gillespie *et al.* 2009]. However, the relationships between the contractile activity of individual myocytes and the generation of afferent nerve activity in normal and diseased bladder remain largely to be established [Drake *et al.* 2001]. Sensory neurons have become increasingly important as targets for medical treatment for OAB/DO. Several studies indicate that BoNT/A appears to be an appealing treatment option for OAB/DO.

Biology and mechanism of botulinum toxin

BoNT/A is a neurotoxin produced by the Gram-positive anaerobic spore-producing organism *Clostridium botulinum*. It is the most lethal naturally occurring toxin known to mankind [Gill, 1982]. There are seven subtypes of BoNT/A (types A–G). Types A and B have been used clinically. BoNT/A was first approved in 1989 for the treatment of strabismus, benign essential blepharospasm and disorders of the VIIth nerve; the use of BoNT has expanded to include gastrointestinal, orthopedic, dermatological, secretory and cosmetic indications as well as in the clinical management of pain in a number of areas [Yokoyama *et al.* 2012]. BoNT/A has been marketed as Botox® in the USA (Allergan, Inc., Irvine, CA, USA) and as Dysport® in the UK (Ipsen Ltd, Slough, Berkshire, UK). From the structural point of view the toxin is a 150 kD amino acid dichain molecule consisting of a light (50 kD) and a heavy chain (100 kD) which are linked by a disulfide bond [Montecucco and Schiavo, 1995].

Although the mechanism of action of BoNT/A has not been clarified completely, it is assumed that BoNT/A inhibits vesicular acetylcholine release from motor nerve terminals by cleaving the SNARE protein SNAP-25, thus having a strong anticholinergic effect [Schiavo *et al.* 1993]. Systemic side effects on neuromuscular structures are therefore expectedly parasympathicolytic.

Regarding the efferent effect, Smith and coworkers have shown significant decreases in the release

of labeled acetylcholine in BoNT/A injection, suggesting that BoNT/A can reduce cholinergic nerve-induced bladder activity [Smith *et al.* 2003b]. Recent studies show that BoNT/A also can inhibit the release of other transmitters and is involved in the regulation of receptor levels in the urothelium [Smith *et al.* 2003a; Datta *et al.* 2010]. In addition to the efferent effects, BoNT/A might also alter afferent sensory inputs. Basic research has proven that BoNT/A has sensory inhibitory effects due to inhibition of urothelial adenosine triphosphate (ATP) release, which might be one mechanism by which BoNT/A reduces DO [Khera *et al.* 2004].

In general, the denervation is temporally limited. The regeneration process relies on the formation of functional neuronal sprouts that reconnect presynaptic nerve endings with their target organs [de Paiva *et al.* 1999].

BoNT/A is considered as a local therapy for NDO. Imaging studies showed that 82.4% of the injected volume of BoNT/A into the bladder wall reached the target area (detrusor) and only a small volume was found in the extraperitoneal fat [Mehnert *et al.* 2009]. It is imaginable that small amounts of BoNT/A leak into the blood circulation and may act at distant sites. Since BoNT/A is a very potent drug, very small amounts may have a measurable effect, especially on neuromuscular structures.

Outcomes of BoNT/A for NDO

Botulinum toxin is mainly used as a highly effective second-line treatment for neurogenic patients, if antimuscarinic treatment has failed. The effectiveness of BoNT/A injections into the detrusor smooth muscle to treat major NDO and neurogenic incontinence has been investigated in several studies (Table 1) [Mehnert *et al.* 2009; Schulte-Baukloh *et al.* 2002; Kessler *et al.* 2005].

The application of BoNT/A in NDO was pioneered by Schurch and colleagues [Schurch *et al.* 2000b]. BoNT/A (200 or 300 IE; Botox, Allergan) was injected into 31 patients with SCI and urodynamically proven NDO. Urodynamically proven significant increases in mean maximum bladder capacity (MBC; $p < 0.016$) and a significant decrease in mean maximum detrusor voiding pressure (MDP; $p < 0.016$) compared with baseline measurement were observed. A significant increase in mean post-void residual urine volume before and after treatment could be demonstrated (261.8–490.5 ml). A total of 17 of 19 patients were completely continent at 6 weeks follow up. Overall follow up, 11 patients showed ongoing improvement in bladder function at 16 and 36 weeks. The injection lasted for at least 9 months. No side effects were observed.

Since then, several studies have approved the efficiency of BoNT/A in the treatment of NDO in adults as well as in children [Apostolidis *et al.* 2009; Reitz and Schurch, 2004; Game *et al.* 2009]. Some preliminary and current studies are summarized in Table 1.

Another preliminary study recruited 17 children with urodynamic verified NDO due to myelomeningocele [Schulte-Baukloh *et al.* 2003]. All cohorts have been resistant to anticholinergic medication. Schulte-Baukloh and colleagues reported that intravesical injection significant improved urodynamic parameters from baseline to follow-up cystometry. Mean reflex volume and MBC increased after 4 weeks and 3 months ($p < 0.01$). MDP significantly decreased after 4 weeks ($p < 0.01$). No side effects were reported. The beneficial effects of BoNT/A lasted up to 6 months.

Schurch and colleagues performed the first double-blind, randomized, placebo-controlled phase II clinical trial on the safety and efficacy of two doses of BoNT/A (200 or 300 U Botox®) *versus* saline injections on urodynamic parameters and UI episodes by NDO of predominantly spinal cord origin [Schurch *et al.* 2005]. Following treatment there were significant decreases in incontinence episodes of approximately 50% at all time points in the two BoNT/A groups, except weeks 12 and 18 in the 200 U BoNT/A group. Compared with placebo the differences between treatment groups were significantly in favor of the 300 U BoNT/A group at weeks 2 ($p = 0.015$) and 6 ($p = 0.047$) and in favor of the 200 U BoNT/A group at week 24 ($p = 0.019$). In addition, mean MBC as well as impact on quality of life significantly increased from baseline in each BoNT/A group at all post-treatment time points ($p \leq 0.020$), although there were no significant changes in the placebo group. Also MDP significantly decreased to a greater extent in the BoNT/A groups compared with placebo at all post-treatment visits.

Two years later, Schurch and colleagues evaluated the effects of BoNT/A detrusor injection on

Table 1. Review of the literature with comparison of previous studies of intravesical botulinum toxin in neurogenic disease (Schurch, 2000a).

Study	Sample Size	Diagnosis	Age (years)	Disease duration (months)	Treatment and dose (BoNT/A/placebo)	Injection sites	Outcome measures	Follow up (weeks)	Success %
Schurch *et al.* [2000]	21	SCI	36.7	60.2	200/300	20/30	UD, clinical parameters	6, 16, 36	89
Schulte-Baukloh *et al.* [2003]	20	Menigo myelocele	10.8	lifelong	12 U/kg, max. 300	30-50	UD, clinical parameters	2,4,12, 24	100
Schurch *et al.* [2005]	59	SCI 89.9%/ MS 6	41	63	200/300/Placebo	30	UD, UI- episodes	2,6,12,18,24	82.2
Schurch *et al.* [2007]	59	SCI 53 MS 6	41.6	63	200/300/Placebo	30	I-QOL	2,6,12,18,24	86.4 77.3
Reitz *et al.* [2007]	20	SCI 18 MS 2	41.1	132	300	30	UD, clinical parameters	4	Improve
Pannek *et al.* [2010]	27	SCI 27	34.5	62.9	300	30	UD parameters	4 after each injection	74
Game *et al.* [2010]	109	SCI 4 MS 87 Spina bifida 5 Others 13	48.2	NA	300	30	IIQ-7, UDI-6, EQ-5D	4 after each injection	Improve
Abdel-Meguid [2010]	38	SCI 38	25	NA	300 Detrusor 200 Detrusor/100 trigone	30	UI, IPSS, UD, clinical parameters, AEs	2,8,12,18	52.4 80.9
Herschorn *et al.* [2011]	57	SCI 38 MS 19	42.8	NA	300 /Placebo	30	UI-episodes ICIQ/I-QOL	6, 12, 24, 36,48,60	100
Cruz *et al.* [2011]	275	SCI 121 MS 154	46	NA	200/300/Placebo	30	UI-episodes UD I-QOL	2,6,12	100
Ginsberg *et al.* [2012]	416	SCI 189 MS 227	46	168	200/300/Placebo	30	UI-episodes UD I-QOL	6	79
Kennelly *et al.* [2012]	387	SCI 157 MS 228	46.4	96	200/300	30	UI-episodes/week	2, 6, 12	94 55

NA not available; SCI, spinal cord injury; MS, multiple sclerosis; UD, urodynamics; UI, urinary incontinence; I-QOL, Incontinence Quality of Life questionnaire; IIQ-7, incontinence impact questionnaire-7; UDI-6, Urogenital Distress Inventory-6; EQ-5D, EuroQol-5D questionnaire; IPSS, International Prostate Syndrome Score; AE, adverse event, ICIQ, International Consultation on Incontinence Questionnaire.

health-related quality of life in 59 patients (SCI, n = 53; MS, n = 6) using the Incontinence Quality of Life questionnaire (I-QOL) [Scurch *et al.* 2007]. The study was a randomized, double-blind, multicenter, placebo-controlled trial and demonstrated a significant I-QOL score increase from screening with BoNT/A 300 U and 200 U compared with placebo at all-time points ($p < 0.05$). The result of this study indicated that BoNT/A is an effective and well-tolerated treatment for improving the health-related quality of life for patients.

Another randomized, double-blind, multicenter trial detailed the efficacy of BoNT/A injection for NDO and UI in 57 patients with SCI and MS [Herschorn *et al.* 2011]. Despite current antimuscarinic treatment, patients were randomized to BoNT/A 300 U (n = 28) or saline placebo (n = 29) via cystoscopic injection at 30 injection sites, sparing the trigone. Patient response to treatment was assessed using daily UI (the primary end point) frequency on 3-day voiding diary, the International Consultation on Incontinence Questionnaire (ICIQ), the urinary I-QOL and urodynamics at week 6. At week 36 all patients were offered open-label BoNT/A 300 U. A significantly lower mean daily frequency of UI was observed in the BoNT/A group compared with the placebo group at weeks 6 ($p < 0.0001$), 24 ($p = 0.0007$) and 36 ($p = 0.0112$). In addition, urodynamic parameters showed significant differences between BoNT/A and placebo in median reflex detrusor volume at first contraction at week 6 ($p = 0.0026$), maximum detrusor pressure during filling at weeks 6, 24 and 36 ($p \leq 0.08$) and in maximum cystometric capacity at weeks 6 and 24 ($p \leq 0.031$). Assessment using ICIQ revealed significantly more favorable scores for BoNT/A than for placebo in frequency and urine leakage at weeks 6 and 24. After open-label injection similar improvements were seen in patients previously randomized.

Similarly, Cruz and colleagues reported successful results of BoNT/A for NDO of a multicenter, randomized, double-blind, placebo-controlled phase III clinical trial [Cruz *et al.* 2011]. Patients with urge incontinence and NDO due to MS (n = 154) or SCI (n = 121) were recruited. Patients received intradetrusor injections of BoNT/A 200 U (n = 92), 300 U (n = 91) or placebo (n = 92). The injection of 200 and 300 U BoNT/A significantly reduced urge incontinence episodes ($p < 0.01$) compared with placebo at week 6. Improvements in MBC, MDP and I-QOL at week 6 were significantly greater with both BoNT/A doses than with placebo ($p < 0.001$). No differences in results were observed in MS and SCI populations. The effectiveness of the therapy was significantly longer (7 months) compared with placebo ($p < 0.001$). A significant increase in post-void residual volume was observed in patients not using clean intermittent catheterization (CIC) prior to treatment, and 12%, 30% and 42% of patients in the placebo, 200-U and 300-U groups, respectively, initiated CIC post-treatment. No systematic side effects were observed.

Another recent multicenter, double-blind, randomized, placebo-controlled phase III clinical trial by Ginsberg and colleagues reported the significant benefit of BoNT/A (200 and 300 U) compared with placebo in patients with NDO and UI due to MS and SCI [Ginsberg *et al.* 2012]. The three groups consisted of placebo (n = 149), 200 U BoNT/A (n = 135) and 300 U BoNT/A (n = 132). Patients were followed up for 52 weeks. In both BoNT/A groups, mean UI as well as MBC, MDP and I-QOL improved significantly compared with the placebo group ($p < 0.001$). Median time to patient retreatment request was greater for BoNT/A than for placebo (8.5 *versus* 3 months). No significant differences were observed between the results of the two BoNT/A groups. The risk of CIC due to urinary retention ascended with high doses of BoNT/A. However, CIC should always be considered in neurogenic patients treated with BoNT/A, especially when high doses are used [Karsenty *et al.* 2008; Kuo, 2006].

Until now there have been only a few studies evaluating the long-term effects of repeated BoNT/A injection on bladder function. The effect of BoNT/A treatment on clinical outcome and urodynamic parameters and quality of life was studied regarding repeated BoNT/A injections (at least five, injection interval ranging from 6.6 to 14.9 months) [Reitz *et al.* 2007; Game *et al.* 2010]. Pannek and colleagues reported long-term efficacy, with 74% avoiding major surgical procedures and suggestions of a decreased detrusor strength due to repeated BoNT/A injections [Pannek *et al.* 2010].

Concerning long-term efficacy and safety of repeat BoNT/A injections in patients with UI due to neurogenic (MS and SCI) DO, recently Kennelly and colleagues presented an interim

analysis of 387 patients (SCI, 200 U n = 83, 300 U n = 74; MS, 200 U n = 119, 300 U n =111) focusing on the results of repeated treatment for up to five treatment cycles [Kennelly *et al.* 2012]. Of these patients, 387, 336, 241, 113 and 46 patients received one, two, three, four and five BoNT/A treatments, respectively. Patients received repeat treatment if the treatment criteria (minimum of 12 weeks since the previous injection, ≥1 UI episode within 3 days) had been fulfilled. Episodes of UI/week were significantly decreased at week 6. The decreases from baseline were −22.7, −23.3, −23.1, −25.3 and −31.9 regarding 200 U BoNT/A and −23.8, −25.0, −23.6, −24.1 and −29.5 regarding 300 U BoNT/A in cycles 1–5, respectively. The proportion of dry (100% reduction) patients ranged from 36% to 55%. The time to patients request for repeat treatment over cycles 1 and 2 remained consistent (~36 weeks). Because the long-term study is ongoing, several patients in treatment cycles 3–5 had not yet requested or received their next treatment. However, a trend toward a slight reduction in time to patients' request for repeat treatment was observed.

Despite the fact that more than 80% of the patients were satisfied or very satisfied with the BoNT/A effect [Kessler *et al.* 2005], the individual indication and the temporally limited effectiveness of BoNT/A should be considered carefully. However, nuances on dosage, interval between injection, injection technique, injection localization, as well as different impact between gender and diseases, are still not completely understood. Further investigations are warranted in larger placebo-controlled, randomized studies.

Injection technique

Intravesical BoNT/A injection can be performed using a rigid or flexible cystoscope under general, spinal, local or without any anesthesia. The manner of anesthesia and cystoscopy depends on the patient status and the institution preferences. The injection should be gently given into the detrusor muscle. Penetration of the bladder wall and an injection into the perivesical tissues should be avoided.

In the first report of intravesical BoNT/A, the investigators injected directly into the detrusor muscle at 30 injecting sites, avoiding the trigone [Schurch *et al.* 2000a]. The majority of published data are based on similar injection techniques; only the number of injection sites varies, from 10 to 50 [Karsenty *et al.* 2008; Rapp *et al.* 2007]. The decision to avoid the trigone was multifactorial, including a desire to avoid inducing reflux to the upper tract. In addition, it was believed that injection of the dense trigone innervation from both sensory, adrenergic and noncholinergic pathways might complicate the efficacy analysis of a cholinergic blockade [Rapp *et al.* 2007]. Two studies reported successful outcomes utilizing a BoNT/A injection with trigone inclusion [Smith *et al.* 2005; Rackley *et al.* 2005], but no direct comparison was made with patients receiving trigone-sparing injections.

Lucioni and colleagues investigated the benefit of trigone inclusion during BoNT/A injection [Lucioni *et al.* 2006]. A total of 40 patients with NDO refractory to anticholinergic treatment underwent trigone or trigone-sparing injection of BoNT/A (300 U). No difference between the treatment arms was found.

In contrast, the results of Abdel-Meguid from a randomized, prospective study, which evaluated the results of 300 U BoNT/A injection excluding the trigone *versus* 200 U BoNT/A into the bladder wall and further 100 U BoNT/A into the trigone showed significant differences in complete dryness in favor of the trigone injection [Abdel-Meguid, 2010]. Despite these findings, further investigation is needed to determine whether trigone injection is associated with improved urodynamic outcomes or may be more appropriately used in neurogenic or non-neurogenic patients.

Safety

Nearly all studies reported an excellent safety profile of BoNT/A intradetrusor injection. The main reported adverse events were either transient or easily manageable (i.e. mild hematuria, injection site pain, urinary tract infection) or, especially in NDO, anticipated and intended (i.e. urinary retention) [Apostolidis *et al.* 2009; Karsenty *et al.* 2008; Shaban and Drake, 2008]. Urinary tract infections have been reported between 2% and 32% of patients treated, and are usually associated with a large post-void residual urine volume [Karsenty *et al.* 2008]. On the other hand Game and colleagues reported that BoNT/A treatment reduced the incidence of symptomatic urinary tract infection in neurogenic bladder patients by 88% [Game *et al.* 2008]. However,

some studies report general muscle weakness after intradetrusor BoNT/A injections, suggesting leakage of BoNT/A into the blood circulation [De Laet and Wyndaele, 2005]. Grosse and colleagues documented four patients suffering from brief muscle weakness after BoNT/A with symptoms lasting 2–8 weeks [Grosse *et al.* 2005]. Concerning repeated intradetrusor BoNT/A injections, Reitz and colleagues investigated the safety and valuable treatment option for NDO over a period of several years [Reitz *et al.* 2007]. The patients (n = 20; SCI, n = 18; MS, n = 2) received at least five intravesical BoNT/A injections. No toxin-related side effects were observed after the first and repeated injections. Clinical and urodynamic parameters improved significantly after the first injection and remained constant after repeat injections. Finally, manipulations of the lower urinary tract always include an increased risk of autonomic dysreflexia in SCI patients with lesions at or above Th6 [Apostolidis *et al.* 2009].

Conclusion

In selected patients with NDO, BoNT/A injection offers an important therapeutic alternative to antimuscarinics treatment or healthcare. BoNT/A decreases not only the overactivity, but also improves quality of life. The improvement of injection dose and techniques over the last decade have considerably reduced failure as well as adverse events and have made BoNT/A an effective, minimally invasive treatment for NDO. But still further studies are required to assess the durability and quality of BoNT/A and to further optimize dose, technique, injection sites as well as intervals of retreatment corresponding to any neurogenic or non-neurogenic LUTD.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors have no conflicts of interest to declare.

References

Abdel-Meguid, T. (2010) Botulinum toxin A injections into neurogenic overactive bladder- to include or exclude the trigone? A prospective, randomized, controlled trial. *J Urol* 184: 2423–2428.

Abrams, P., Cardozo, L., Fall, M. Griffiths, D., Rosier, P., Ulmsten, U. *et al.* (2002) The standardisation of terminology of lower urinary tract function: Report from the Standardisation Subcommittee of the International Continence Society. *Neurourol Urodyn* 21: 167.

Apostolidis, A., Dasgupta, P., Denys, P., Elneil, S., Fowler, C., Giannantoni, A. *et al.* (2009a) 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* 55: 100–119.

Cruz, F., Herschorn, S., Alicotta, P. Brin, M., Thompson, C., Lam, W. *et al.* (2011) Efficacy and safety of onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity: a randomized, double-blind, placebo-controlled trial. *Eur J Urol* 60: 742–750.

Datta, S., Roosen, A., Pullen, A. Popat, R., Rosenbaum, TP., Elneil, S. *et al.* (2010) Immunohistochemical expression of muscarinic receptors in the urothelium and suburothelium of neurogenic and idiopathic overactive human bladders, and changes with botulinum neurotoxin administration. *J Urol* 184: 2578–2585.

deGroat, W. (1997) A neurologic basis for the overactive bladder. *Urology* 50(S6A): 36.

De Laet, K. and Wyndaele, J. (2005) Adverse events after botulinum A toxin injection for neurogenic voiding disorders. *Spinal Cord* 43: 397–399.

de Paiva, A., Meunier, F., Molgo, J. Aoki, KR., Dolly, JO. *et al.* (1999) Functional repair of motor endplates after botulinum neurotoxin type A poising: biphasic switch of synaptic activity between nerve sprouts and their parent terminals. *Proc Natl Acad Sci USA* 96: 3200–3205.

Drake, M., Mills, I. and Gillespie, J. (2001) Model of peripheral autonomous modules and a myovesical plexus in normal and overactive bladder function. *Lancet* 358: 437.

Fowler, C., Griffiths, D. and de Groat, W. (2008) The neural control of micturition. *Nat Rev Neurosci* 2008; 9: 453–466.

Game, X., Castel-Lacanal, E., Bentaleb, Y. Thiry-Escudié, I., De Boissezon, X., Malavaud, B. *et al.* (2008) Botulinum toxin A detrusor injections in patients with neurogenic detrusor overactivity significantly decrease the incidence of symptomatic urinary tract infection. *Eur J Urol* 53: 613–618.

Game, X., Khan, S., Panicker, J. Kalsi V., Dalton, C., Elneil, S. *et al.* (2010) Comparison of the impact on health-related quality of life of repeated detrusor injections of botulinum toxin in patients with

idiopathic or neurogenic detrusor overactivity. *Br J Urol* 107: 1786.

Game, X., Mouracade, P., Chartier-Kastler, E. Viehweger, E., Moog, R., Amarenco, G., Denys, P. *et al.* (2009) Botulinum toxin A intradetrusor injections in children with neurogenic detrusor overactivity/neurogenic overactive bladder: a systematic review.
J Ped Urol 5: 156–164.

Gill, D. (1982) Bacterial toxins: A table of lethal amounts. *Microbiol Rev* 46: 86–94.

Gillespie, J., van Koeveringe, G., de Wachter, S. de Vente, J. *et al.* (2009) On the origins of the sensory output from
the bladder: the concept of afferent noise. *BJU Int* 103: 1324.

Ginsberg, D., Gousse, A., Keppenne, V. Sievert, KD., Thompson, C., Lam, W. *et al.* (2012) Phase 3 efficacy and tolerability study of onabotulinumtoxinA for urinary incontinence from neurogenic detrusor overactivity. *J Urol* 187: 2131–2139.

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

Herschorn, S., Gajewski, J., Ethans, K. Carlson, K., Bailly, G., Bard, R. *et al.* (2011) Efficacy of botulinum toxin A injection for neurogenic detrusor overactivity and urinary incontinence:
a randomized, double-blind trial. *J Urol* 185: 2229–2235.

Karram, M. (1999) Detrusor instability and hyperreflexia. In: Walters, M. and Karram, M. (eds), *Clinical Urogynecology*, 2nd edn. St. Louis, MO: Mosby.

Karsenty, G., Denys, P., Amarenco, G. De Seze M., Gamé, X., Haab, F., *et al.* (2008) Botulinum toxin A (Botox) intradetrusor injections in adults with neurogenic detrusor overactivity/neurogenic overactive bladder: a systematic literature review. *Eur Urol* 53: 275–287.

Kennelly, M., Dmochowski, R., Ethans, K. Karsenty, G., Schulte-Baukloh, H., Jenkins, B. *et al.* (2012) Long-term efficacy and safety of onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity: an interim analysis. *J Urol* 81: 491–497.

Kessler, T., Danuser, H., Schumacher, M. Studer, UE., Burkhard, FC. *et al.* (2005) Botulinum A Toxin injection into detrusor: An effective treatment in idiopathic and neurogenic detrusor overactivity? *Neurourol Urodynam* 24: 231–236.

Khera, M., Somogyi, G., Kiss, S. Boone, TB., Smith, CP. *et al.* (2004) Botulinum toxin A inhibits ATP release from bladder urothelium after chronic spinal cord injury. *Neurochem Int* 45: 987–993.

Kruse, M., Mallory, B., Noto, H. Roppolo, JR., de Groat, WC. *et al.* (1991) Properties of the descending limb of the spinobulbospinal micturition reflex pathway in the cat. *Brain Res* 556: 6–12.

Kuo, H. (2006) Will suburothelial injection of small dose of botulinum A toxin have similar therapeutic effects and less adverse events for refractory detrusor overactivity? *Urology* 68: 993–997.

Lucioni, A., Rapp, D., Gong, E. Fedunok, P., Bales, GT. *et al.* (2006) Intravesical botulinum type A toxin injection in patients with overactive bladder: trigone *versus* trigone-sparing injection. *Can J Urol* 13: 3291–3295.

Mangera, A., Andersson, K., Apostolidis, A., Chapple, C., Dasgupta, P., Giannantoni, A. *et al.* (2011) Contemporary management of lower urinary tract disease with botulinum toxin A: a systematic review of Botox (onabotulinumtoxinA) and Dysport (abobotulinumtoxinA). *Eur Urol.* 4: 784–795.

Mehnert, U., Boy, S., Schmid, M. Reitz, A., von Hessling, A., Hodler, J. *et al.* (2009) A morphological evaluation of botulinum neurotoxin A injections into the detrusor muscle using magnetic resonance imaging. *World J Urol* 27: 397–403.

Montecucco, C. and Schiavo, G. (1995) Structure and function of tetanus and botulinum neurotoxins. *Q Rev Biophys* 28: 423–472.

Pannek, J., Goecking, K. and Bersch, U. (2009) Long-term effects of repeated intradetrusor botulinum neurotoxin A injections on detrusor function in patients with neurogenic bladder dysfunction. *Br J Urol* 104: 1246–1250.

Rackley, R., Frenkl, T. and Abdelmalak, J. (2005) Botulinum toxin: the promise of therapy for complex voiding dysfunction. *Cont Urol* 2: 38–52.

Rapp, D., Lucioni, A., Bales, G. *et al.* (2007) Botulinum toxin injection: a review of injection principles and protocols. *Int Braz J Urol* 33: 132–141.

Reitz, A., Denys, P., Fermanian, C. Schurcb, B., Comperat, E. and Chartier-Kastler, E. (2007) Do repeated intradetrusor botulinum toxin type A injections yield valuable results? Clinical and urodynamic results after five injections in patients with neurogenic detrusor overactivity. *Eur J Urol* 5: 1729–1735.

Reitz, A. and Schurch, B. (2004) Intravesical therapy options for neurogenic overactivity. *Spinal Cord* 42: 267–272.

Schiavo, G., Santucci, A., Dasgupta, B. Mehtad, P., Jontesd, J Benfenati, F *et al.* (1993) Botulinum neurotoxins serotypes A and E cleave SNAP-25 at distinct COOH-terminal peptide bonds. *FEBS Lett* 335: 99–103.

Schulte-Baukloh, H., Michael, T., Schobert, J. Stolze, T., Knipsel, HH. *et al.* (2002) Efficacy of botulinum-a toxin in children with detrusor hyperreflexia due to myelomeningocele: preliminary results. *J Urol* 59: 325–327.

Schulte-Baukloh, H., Michael, T., Stürzebecher, B. Knispel, HH. *et al.* (2003) Botulinum A toxin detrusor injection as a novel approach in the treatment of bladder spasticity in children with neurogenic bladder. *Eur Urol* 44: 139–143.

Schurch, B., Denys, P., Kozma Kozma, CM., Reese, PR., Slaton, T., Barron, R. *et al.* (2007) Botulinum toxin A improves quality of life of patients with neurogenic urinary incontinence. *Eur Urol* 52: 850–859.

Schurch, B., de Seze, M., Denys, P. Chartier-Kastler, E., Haab, F., Everaert, K. *et al.* (2005) Botulinum toxin type A is a safe and effective treatment for neurogenic urinary incontinence: result of a single treatment randomized, placebo controlled 6-month study. *J Urol* 174: 196–200.

Schurch, B., Schmid, D. and Stohrer, M. (2000a) Treatment of neurogenic incontinence with botulinum toxin A. *N Engl J Med* 342: 665.

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

Shaban, A. and Drake, M. (2008) Botulinum toxin treatment for overactive bladder: risk of urinary retention. *Curr Urol Rep* 9: 445–451.

Smith, C., Boone, T., de Groat, W. Chancellor, MB., Somogyi, GT, *et al.* (2003a) Effect of stimulation intensity and botulinum toxin isoform on rat bladder strip contractions. *Brain Res Bull* 61: 165–171.

Smith, C., Franks, M., McNeil, B. Ghosh, R., de Groat, WC., Chancellor, MB. *et al.* (2003b) Effect of botulinum toxin A on the autonomic nervous system of the rat lower urinary tract. *J Urol* 169: 1896–1900.

Smith, C., Nishiguchi, J., O'Leary, M Yoshimura, N. and Chancellor, MB. (2005) Single-institution experience in 110 patients with botulinum toxin A injection into bladder or urethra. *J Urol* 65: 37–41.

Yokoyama, T., Chancellor, MB., Oguma, K. Yamamoto, Y., Suzuki, T., Kumon, H., *et al.* (2012) Botulinum toxin type A for treatment of lower urinary tract disorders. *J Urol* 19: 202–215.