available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Review – Neuro-urology

Recommendations on the Use of Botulinum Toxin in the Treatment of Lower Urinary Tract Disorders and Pelvic Floor Dysfunctions: A European Consensus Report

Apostolos Apostolidis [a,*], *Prokar Dasgupta* [b], *Pierre Denys* [c], *Sohier Elneil* [d], *Clare J. Fowler* [e], *Antonella Giannantoni* [f], *Gilles Karsenty* [g], *Heinrich Schulte-Baukloh* [h], *Brigitte Schurch* [i], *Jean-Jacques Wyndaele* [j]

[a] *2nd Department of Urology, Papageorgiou Hospital and Centre for Study of Continence and Pelvic Floor Dysfunctions, Aristotle University of Thessaloniki, Thessaloniki, Greece*
[b] *Department of Urology, Guy's and St. Thomas' Hospitals and GKT Medical School, London, UK*
[c] *Department of Physical Medicine and Rehabilitation, Raymond Poincare Hospital, University of Versailles, Versailles, France*
[d] *Department of Uro-Neurology, National Hospital for Neurology and Neurosurgery, UCLH, London, UK*
[e] *Department of Uro-Neurology, Institute of Neurology, UCL, London, UK*
[f] *Department of Urology, University of Perugia, Perugia, Italy*
[g] *Department of Urology, Sainte Marguerite Hospital, University of Mediterranée, Marseilles Faculty of Medicine, Marseilles, France*
[h] *Department of Urology, St. Hedwig Hospital, Medical School of Charité University Hospital, Berlin, Germany*
[i] *Neurourology, University Hospital Balgrist, Zurich, Switzerland*
[j] *Department of Urology, University Hospital UZA, Antwerp, Belgium*

Article info

Article history:
Accepted September 8, 2008
Published online ahead of print on September 17, 2008

Keywords:
Botulinum toxin
Bladder
Urethra
Children
Prostate
Pelvic floor
Mechanism of action

Abstract

Context: The increasing body of evidence and number of potential indications for the use of botulinum neurotoxins (BoNTs) in the lower urinary tract (LUT) underlines the pressing need for evidence-based guidelines.
Objective: A European expert panel consensus conference was convened with the main aim of evaluating the evidence and clinical considerations for the use of BoNTs in the treatment of urologic and pelvic-floor disorders and to propose relevant recommendations.
Evidence acquisition: The quality of evidence from fully published English-language literature in the PubMed and EMBASE databases was assessed using the European Association of Urology (EAU) levels of evidence (LoE). Recommendations were graded and approved by a unanimous consensus of the panel.
Evidence synthesis: The use of botulinum neurotoxin type A (BoNTA) is recommended in the treatment of intractable symptoms of neurogenic detrusor overactivity (NDO) or idiopathic detrusor overactivity (IDO) in adults (grade A). Caution is recommended in IDO because the risk of voiding difficulty and duration of effect have not yet been accurately evaluated. Repeated treatment can be recommended in NDO (grade B). The depth and location for bladder injections should be within the detrusor muscle outside the trigone (grade C). Dosage in children should be determined by body weight, with caution regarding total dose if also being used for treatment of spasticity, and minimum age (grade B). Existing evidence is inconclusive for recommendations in neurogenic detrusor–sphincter dyssynergia, bladder pain syndrome, prostate diseases, and pelvic-floor disorders. The use of BoNTA in the LUT with the current dosages and techniques is considered to be safe overall (grade A).
Conclusions: The consensus committee recommends larger placebo-controlled and comparative trials to evaluate the efficacy of single and repeat injections, the duration of effect, the optimal dosage and injection technique, the timing for repeat injection, and the short- and long-term safety of the treatment in LUT and pelvic-floor disorders.

* Corresponding author. 2nd Department of Urology, Aristotle University of Thessaloniki, Papageorgiou Hospital, Ring Road, Nea Efkarpia, 56403 Thessaloniki, Greece.
E-mail address: zefxis@yahoo.co.uk (A. Apostolidis).

0302-2838/$ – see back matter doi:10.1016/j.eururo.2008.09.009

1. Introduction

The use of botulinum neurotoxins (BoNTs) in the lower urinary tract (LUT) was pioneered as early as 20 yr ago with injections into the urethral sphincter [1] reducing bladder-voiding pressures, urethral pressures, and postvoid residual (PVR) urine. Over the past 10 yr, the use of botulinum neurotoxin type A (BoNTA) has revolutionised the treatment of intractable symptoms associated with the overactive bladder (OAB) [2]. The use of BoNTA has also expanded into pelvic pain syndromes, including the bladder pain syndrome (BPS) [3], as well as into benign prostatic diseases [4]. The body of clinical evidence to support such interventions is rapidly growing, and preclinical and translational studies confirm its potential as a treatment modality. BoNTA, however, remains an unlicensed treatment in LUT and pelvic-floor disorders. The increasing number of potential indications together with a wide variation of injected doses, injection techniques, treatment, and follow-up protocols underline the pressing need for evidence-based guidelines. For that purpose, a European expert panel consensus conference was convened with the aims of (1) evaluating the evidence for and clinical considerations in the use of BoNTs in treating LUT and pelvic floor disorders, (2) considering possible roles for future research of BoNTs in treating other urologic conditions, and (3) proposing recommendations for the use of BoNTs in the clinical areas of interest. Such attempts have previously been made at a national level or they only addressed a specific application, usually the neurogenic bladder [5–7].

2. Evidence acquisition

A consensus panel of the European researchers with a high volume of key publications on the use of BoNTs in urologic and pelvic-floor disorders was convened in January 2008 in Thessaloniki, Greece.

A systematic review of the PubMed and EMBASE databases for fully published English-language literature was performed by the working panel. In PubMed the search was convened using the medical subject heading (MeSH) term *botulinum toxin* in conjunction with any of the following terms: *bladder, urethra, prostate*, and *pelvic floor*. The limitations *English language* and *human* were subsequently used. The references on *botulinum toxin* and *bladder* were further categorised using the following limitations: *neurogenic, idiopathic, non-neurogenic, overactive, painful*, and *children*. Review articles and published abstracts were identified by limiting for *review* and *abstract*, respectively. The reference list of review and original papers were reviewed to identify any missed papers. A similar search strategy was applied in EMBASE using identical EMTREE terms.

All original articles were reviewed for primary and secondary outcomes, injection protocol characteristics, and adverse events. For each clinical variable, percent changes were calculated from results reported at the time of the latest follow-up with an adequate number of patients, allowing for comparisons with baseline values. Abstracts were excluded from data extraction because they are not peer reviewed, thus their methods and results could not be evaluated. Data for each BoNT application were extracted by one author and quality controlled by another.

The consensus panel met in closed session; relevant data were presented, and the quality of evidence and strength of recommendation were graded. The levels of evidence (LoE) and recommendation grades applied were those adopted by the European Association of Urology (EAU) [8] (Tables 1 and 2). The consensus statements were formulated using the Delphi approach (www.carolla.com/wp-delph.htm), and the final recommendations were approved by a unanimous consensus of the panel (Table 3). Final preparation and modifications of the consensus paper were made by electronic communication.

Table 1 – Levels of evidence applied by the European Association of Urology

Level	Type of evidence
1a	Evidence obtained from meta-analysis of randomised trials
1b	Evidence obtained from at least one randomised trial
2a	Evidence obtained from one well-designed controlled study without randomisation
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study
3	Evidence obtained from well-designed nonexperimental studies, such as comparative studies, correlation studies, and case reports
4	Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities

Table 2 – Recommendation grades applied by the European Association of Urology

Grade	Nature of recommendations
A	Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial
B	Based on well-conducted clinical studies but without randomised clinical trials
C	Made despite the absence of directly applicable clinical studies of good quality

3. Evidence synthesis

3.1. *Pharmacology*

Pharmacokinetic studies with BoNTs are not feasible in humans. Animal studies have shown that after injection of BoNTA in skeletal muscles, there is slow muscular diffusion of the complex followed by rapid systemic metabolism and urine excretion (60% excreted within 24 h). The half-life occurs at approximately 10 h.

BoNTA consists of a light chain attached to a heavy chain via a disulfide bond with an associated zinc atom. It is synthesised as a single-chain polypeptide with a molecular weight of 150 kDa, which is then cleft into its active dichain polypeptide form. The heavy chain (about 100 kDa) allows for binding to the neuron and internalisation of the toxin, whereas the light chain (about 50 kDa) actively cleaves SNAP25 (synaptosomal-associated protein with a molecular weight 25 kDa) on the protein complex that is responsible for docking and releasing vesicles containing neurotransmitters [9].

3.2. *Mechanism of action*

The scientific background for the application of BoNTA in the external urethral sphincter in patients with neurogenic detrusor-sphincter dyssynergia (nDSD) [1] was BoNTA's known effect of blocking the presynaptic vesicular release of acetylcholine (ACh) at the neuromuscular junction [9]. Despite clinical evidence from its use in neurologic disorders suggesting an effect of BoNTA on afferent abnormalities [10], weakening of striated musculature has remained an appropriate aim in the management of nDSD and pelvic-floor disorders characterised by excessive and sometimes painful muscle spasms. In neurogenic detrusor overactivity (NDO) as well as in patients with idiopathic detrusor overactivity (IDO), the post-treatment reductions in detrusor pressures during both phasic involuntary contractions and on voiding [11–13] are evidence for an effect of BoNTA on the motor innervation of the detrusor, although the neurologic deficit which additionally affects voiding efficiency in the NDO group may partly explain the high rate of post-treatment clean intermittent self-catheterisations (CISC).

Patients, however, also report a rapid reduction in their sensations of urgency, which are associated with involuntary detrusor overactivity (DO) [14,15]. Although the exact nature and cause of urgency remains to be elucidated, aberrant afferent activity is thought to be a significant cause of spinal NDO [16], and much less is known about the role of afferents in IDO. In both neural and bladder tissue, BoNTA affected the release of numerous sensory transmitters other than ACh, including adenosine triphosphate (ATP), substance P, calcitonin gene-related peptide (CGRP), and glutamate, which may be dependent on the same mechanism of vesicle trafficking [17], and reduced the levels of sensory receptors [18] and nerve growth factor (NGF) in the bladder wall [19]. Thus, it seems highly probable that in addition to a direct effect on detrusor motor innervation, BoNTA also modulates intrinsic bladder reflexes through a multimodal effect on sensory pathways (Fig. 1) [17]. Such mechanisms may contribute to the efficiency of this treatment and partly explain how it affects abnormal detrusor contractions more markedly than voluntary bladder emptying.

3.3. *Adult detrusor overactivity and overactive bladder*

An expert panel at the 2nd International Consultation on Incontinence in 2004 designated a LoE 2 and recommendation grade B for the use of BoNTA in OAB symptoms and DO [20]. Several review articles and a Cochrane library review support the use of BoNTs in adult DO and OAB, limitations being the small number and size of existing randomised controlled trials (RCTs) [7].

3.3.1. *Adult neurogenic detrusor overactivity*

BoNTA decreased symptoms of intractable NDO in 2 placebo-controlled trials (LoE 1b) (1 with Botox, 1 with Dysport) [12,21], 1 active comparator–controlled trial (LoE 1b) [22], and 22 open-label (LoE 3) studies [2,11,13,19,23–42]. Another RCT studied the effect of botulinum toxin type B (BoNTB, Myobloc) on refractory DO but included only three NDO patients [43]. Treatment of a total of 1018 NDO patients has

Table 3 – Recommendations on the use of botulinum neurotoxins (BoNTs) in the treatment of intractable symptoms of lower urinary tract (LUT) and pelvic-floor disorders, as unanimously agreed by a European consensus panel

Recommendations on the use of BoNTs in the treatment of intractable symptoms of LUT and pelvic-floor disorders	Grade
NDO	
Use BoNTA to treat refractory NDO in patients willing to use CISC.	A
The aim of the treatment is to improve symptoms, urodynamic risk factors for renal impairment, or quality of life in patients with spinal NDO.	A
The diagnosis of NDO should follow the EAU guidelines (ie, urodynamic assessment is mandatory).	A
Patients should be told the treatment does not last indefinitely but should have a mean duration of 8 mo.	A
Repeated treatment has been shown to be efficacious.	B
IDO/OAB	
Use BoNTA to treat refractory IDO in patients willing to use CISC.	A
Use caution because the risk of voiding difficulty as well as the duration of effect has not been accurately evaluated to date. Future studies should address the benefit–risk ratio for the best minimal dosage.	
All patients should accept in writing the possible need to perform CISC following treatment.	A
Residual volumes should be measured regularly for the first month starting at the first week.	A
Patients should be told that the treatment does not last indefinitely but has a mean duration of 6 mo.	A
Comparison of injection techniques	
The dilution of Botox should be 10 U/ml per site; thus, the number of injection sites depends on the total dosage being administered (ie, 30 sites for a dosage of Botox 300 U in NDO). The optimum dose for dilution of Dysport has yet to be established.	B
The choice of flexible or rigid cystoscope should be left to local expertise.	C
The depth and location for injections should be within the detrusor muscle outside the trigone.	C
Detrusor injections in children	
Dose range should be determined by body weight: 5–10 U/kg body weight up to a maximum dosage of Botox 300 U has been shown to be effective and safe. Caution is recommended for the total dosage in children also treated for spasticity.	B
A minimum age of 3 yr is suggested because there are little data for younger ages.	C
Other recommendations follow adult NDO indications.	A
BoNTA sphincter injections	
There is LoE 1b for the use of BoNTA in DSD in neurogenic patients, but the clinical value of this has to be studied further before a recommendation can be made.	–
If injection is done, Botox 100 U in 4 ml should be used.	C
Further studies in adults with voiding dysfunction of non-neurogenic origin are needed.	A
Before its use in children is recommended, the longer term clinical value needs to be assessed.	–
BPS	
In the absence of placebo-controlled data in the indication of BPS, it is impossible to recommend the use of BoNTA despite results from open-label studies.	–
Patients should be warned of the possible need to perform CISC or of worsening pain.	C
BPH associated with LUTS	
Currently, there is insufficient data to recommend this promising treatment for use of BoNTA for bladder-outlet obstruction due to BPH indication.	–
Further placebo-controlled studies are needed.	A
Pelvic-floor disorders	
Insufficient evidence exists on which to base clinical advice.	–
There is a need for robust clinical trials to prove that this agent is truly efficacious in this disparate group of patients.	A
Safety in urological applications	
BoNT can be used in the LUT with the current dosages and techniques; the clinical results show that it is safe overall. Side-effects have been reported, mostly at a low incidence.	A
Further follow-up of safety is necessary because BoNT in other applications has been shown to have histologic, autonomic, and other secondary effects. Similar studies are also needed in urologic treatment.	A
Patients treated for DO should accept beforehand the possible need to perform CIC because increase of residual/retention is the most frequent complication.	A

The highest grade of recommendation was given for the use of BoNTA in NDO and IDO refractory to oral pharmacotherapy in patients willing to perform CISC if needed as well as for the overall clinical safety of the treatment under the currently used dosages and techniques. No recommendations could be made for the use of BoNTs in urethral sphincter disorders, BPS, benign prostate diseases, and pelvic-floor disorders, as the available data were considered inconclusive. Large placebo-controlled and comparative trials are needed in all aspects of BoNT use in the LUT and the pelvic floor.

NDO = neurogenic detrusor overactivity; BoNTA = botulinum neurotoxin type A; DO = detrusor overactivity; CISC = clean, intermittent self-catheterisation; EAU = European Association of Urology; IDO = idiopathic detrusor overactivity; OAB = overactive bladder; LoE = level of evidence; DSD = detrusor-sphincter dyssynergia; BPS = bladder pain syndrome; BPH = benign prostatic hyperplasia; LUTS = lower urinary tract symptoms; CIC = clean intermittent catheterisation.

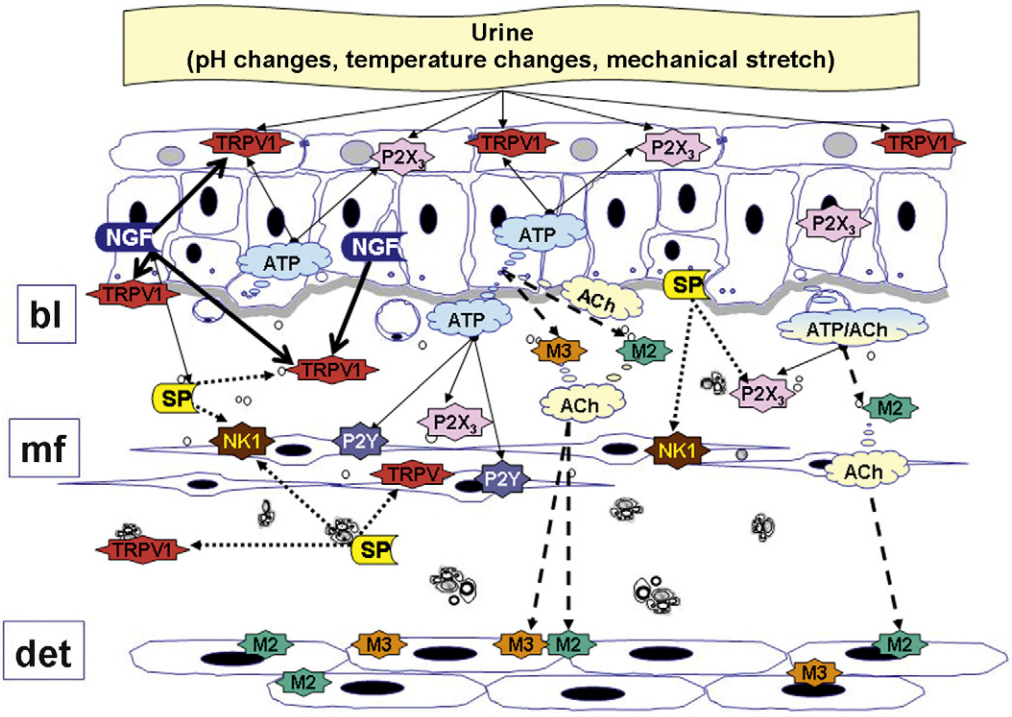

Fig. 1 – Proposed mechanism of action of botulinum toxin type A (BoNTA) injected into the overactive bladder wall. It has been proposed that a complex system of interactions exists between the release of neurotransmitters and actions on respective receptors located on the urothelium and suburothelium, corresponding to pathways of bladder mechanosensation. All connections identified by arrows (see Apostolidis et al [17] for arrow identification) are thought to be upregulated in detrusor overactivity. BoNTA may exert a multimodal effect on those pathways via multiple inhibition of the vesicular release of neurotransmitters and neuropeptides by the urothelium and suburothelial nerves and reduction of the axonal expression of soluble N-ethylmaleimide-sensitive factor attachment receptor (SNARE)-complex–dependent proteins that are thought to be involved in bladder mechanosensation.
Reproduced with permission from Elsevier [17].
bl = basal lamina of urothelium; mf = myofibroblast layer; det = detrusor muscle; TRPV1 = transient receptor potential vanilloid 1; $P2X_3$ = ionotropic purinergic receptor type 3; P2Y = metabotropic purinergic receptors; M2/M3 = muscarinic acetylcholine receptors types 2 and 3; NK1 = neurokinin receptor type 1 (SP receptor); SP = substance P; NGF = nerve growth factor; ACh = acetylcholine; ATP = adenosine triphosphate.

been reported in fully published studies to date. The majority had spinal NDO due to spinal cord injury (SCI) or multiple sclerosis (MS). The summarised results showed that Botox 300 U was the most commonly used dosage. There is no systematic analysis yet available on the efficacy of different dosages. Despite heterogeneous designs, almost all single-injection studies showed significant improvements at the last follow-up (LoE 1b) in such outcomes as incontinence episodes (mean reduction: 69%; range: 32–100%), maximum cystometric capacity (MCC; mean increase: 85%; range: 11–303%), and maximum detrusor pressure ($Pdet_{max}$; mean decrease: 44%; range: 5–83%) (Table 4). The mean percentage of spinal NDO patients who became fully continent was 56.6% (range: 30–87%), but the rate of full return to continence was only 8% in patients with NDO due to cerebrovascular accident. Quality of life (QoL) improved independent of questionnaire used and in both placebo-controlled trials (LoE 1b) (mean improvement: 57%; range: 35–78%). After a rapid onset of effect (4 d) [40], the mean duration of efficacy in single-injection studies was 8 mo (range: 12–36 wk) (Table 4). Repeat treatments showed sustained clinical benefits in open-label studies using up to five injections of Botox or seven injections of Dysport [31,38,41,42] (LoE 3). BoNTA injections provided superior clinical and urodynamic benefits to intravesically instilled resiniferatoxin up to 18 mo after treatment [22] (LoE 1b).

Two independent, double-blind, placebo-controlled, multinational, randomised, phase three studies are currently ongoing to asses the potential use of Botox for the treatment of neurogenic OAB in SCI and MS patients. The studies are evaluating the efficacy, safety profile, as well as the duration of

Table 4 – Studies using botulinum neurotoxin type A (BoNTA) for treatment of intractable symptoms of neurogenic detrusor overactivity (NDO)

Study	No. of patients	BoNT type, dosage	Continence % completely dry/% Δleak episodes	MCC change, %	$Pdet_{max}$ mean % change vs base line	QoL mean % change vs base line	Duration of follow-up	Duration of benefit	LoE
Kalsi et al [40]	16	Botox 300 U	NA/−88 (result at day 4)	NA	NA	NA	4 wk	≥4 wk	3
Kalsi et al [39]	43	Botox 300 U	NA/−77	+303	−33.5	+78 (UDI6-IIQ7)	16 wk (per injection) 1 reinjection	9.7 mo	3
Reitz et al [41]	20	Botox 300 U	85/NA	+130	−83	NA	35 mo (4 reinjections)	≥28 wk (per injection)	3
Del Popolo et al [42]	199	Dysport 500 U, 750 U, 1000 U	95/−95*	+80	NA	+40 (VAS)	75 mo (up to 8 reinjections)	44–52 wk (per injection)	3
Ehren et al* [21]	31	Dysport 500 U	NA/−48	+37.5	−69	NA	26 wk	26 wk	1b
Kalsi et al [35]	63	Botox 300 U	NA/−47	+178	−22	NA	≥15 mo	10 mo	3
Giannantoni et al [27]	23	Botox 300 U	78/−68	+86	−61	NA	12 wk	≥12 wk	3
Karsenty et al [38]	17	Botox 300 U	NA/−100	+43 (first) +32 (last)	−62 (first) −65 (last)	NA	208 wk	39 wk	3
Schulte-Bauklohet al [33]	16	Botox 300 U	NA/NA	+36	−57	35 (UDI-6) 50 (SSI)	24 wk	≥12 wk	3
Kalsi et al [34]	32	Botox 300 U	NA/−85	+166	−54	65 (UDI-6)	16 wk	≥16 wk	3
Ruffion et al [37]	45	Dysport 500 U	30/NA	+74	−20	NA	88 wk	16–17	3
		Dysport 1000 U	75/NA	+82	−49	NA	88 wk	40–44	
Schurch et al [12]	59	Botox 200 U	74/−32	+67	−50	61	24 wk	≥24 wk	1b
		Botox 300 U	53/−58	+32	−38	56 (I-QoL)			
Kuo [36]	24	Botox 200 U	8/NA (CVA 42/NA (SCI)	+28 +45	−27 −34	NA	12 wk	12 wk	3
Klaphajone et al [30]	10	Botox 300 U	50/NA	+23	−24	NA	36 wk	≥16 wk	3
Popat et al [13]	44	Botox 300 U	55/−68	+181	−42	NA	16 wk	≥16 wk	3
Kessler et al [28]	11	Botox 300 U	73/NA	+116	−40	NA	1 wk	22 wk	3
Hajebrahimi et al [32]	10	Botox 400 U	86/NA	+74	−16	NA	12 wk	≥12 wk	3
Smith et al [29]	42	Botox 100–300 U	NA/NA	+61	−10	NA	24 wk	≥24 wk	3
Grosse et al [31]	66	Botox 300 U Dysport 750–1000 U	73/NA	+40	NA	NA	NA	36–44 wk	3
Giannantoni et al [22]	12	Botox 300 U vs RTX	73/−77	+54	−44	NA	112 wk	35 wk (per injection)	1b
Bagi et al [24]	15	Botox 300 U	87/NA	+31	−59	NA	6 wk	30 wk	3
Kuo [26]	30	Botox 200 U	8/NA	+11		51 (IPSS)	12 wk	21 wk	3
Reitz et al [11]	200	Botox 300 U	73/NA	+54 (week 12) +29 (week 36)	−51 (week 12) −28 (week 36)	NA	36 wk	≥36 wk	3
Kennelly et al [23]	10	Botox 300 U	80/NA	+23	−5	NA	24 wk	12–24 wk	3
Schurch et al [2]	21	Botox 200 or 300 U	64/NA	+54	−44	NA	36 wk	≥36 wk	3

Despite heterogeneous designs, all single-injection studies showed significant improvements in a variety of outcomes concerning symptomatology, urodynamics, and quality of life. The LoE for a beneficial effect of BoNTA in NDO is 1b. There is LoE 3 for efficacy of repeat treatments.

MCC = maximum cystometric capacity; $Pdet_{max}$ = maximum detrusor pressure; QoL = quality of life; LoE = levels of evidence; DO = detrusor overactivity; NA = not applicable; UDI6-IIQ7 = Urinary Distress Inventory and Incontinence Impact Questionnaire short forms; VAS = Visual Analogue Scale; UDI-6 = Urinary Distress Inventory short form; SSI = Symptom Severity Index; I-QoL = Urinary Incontinence Quality of Life scale; IPSS = International Prostate Symptom Score; CVA = cerebrovascular accident; SCI = spinal cord injury; RTX = resiniferatoxin.

* Results not included in analysis of means.

Table 5 – Studies using botulinum neurotoxin type A (BoNTA) for treatment of intractable symptoms of non-neurogenic overactive bladder (OAB) or detrusor overactivity (DO)

Study	No. of patients	BoNT type, dosage	% improvement or success	Continence % completely dry/% Δ leak episodes	Frequency change, %	Urgency change, %	MCC change, %	$Pdet_{max}$ change, %	DO resolution, %	QoL 1 reinjectionimprovement, %	Duration of study or benefit	LoE
Jeffery et al [59]	25	Dysport 500 U	–	32/NA	−22	−22	+19	–	40	37	9 mo (study) 6 mo (benefit)	3
Lee et al[b] [52]	10	Purified toxin 50–200 U	89	50/−58	−26	–	+125	−56	–	22	3 mo (study) 6 mo (benefit)	3
Sahai et al [44]	32	Botox 200 U vs placebo	–	70/NA	−40	−53	+45	−49	25	52	6 mo (study)	1b
Kuo [46]	45	Botox 100 U detrusor	80/3 mo	60/NA	−48	−34	+27	−20	–	93	9 mo (study)	2b
		Botox 100 U suburo	42/6 mo	47/NA	+24	−28	+51	+10		80	6 mo (benefit)	
		Botox 100 U base	16/9 mo	53/NA	−40	−50	+12	+9		87		
Ghalayini and Al-Ghazo [53]	16	Dysport 500 U	–	75/NA	−55	–	+36	−26	–	Satisfied: 87.5	5 mo (benefit)	3
Karsenty et al [54]	11	Botox 100 U including trigone	36.4	33.3/NA	−33.3	–	+128	−20	75	–	6 wk (study)	3
Kuo [45]	35	Botox 100 U vs Botox 150 U vs Botox 200 U	77.1	40/NA	–	–	+36, 100 U* +36, 150 U* +47, 200 U*	+6, 100 U* −29, 150 U* –21, 200 U*	–	–	3 mo (study) Benefit: 6.7 mo, 300 U* 5.5 mo, 200 U* 3.5 mo, 100 U* Duration shorter with 100 U*	2b
Lucioni et al [51]	40	Trigone vs nontrigone	63	–/–	–	–	–	–	–	26.5 trigone 23 nontrigone	3 mo (study)	3
Schmnid et al [15]	100	Botox 100 U	88	NA/−86	−50	82, no urgency	+56	–	−74	–	9 mo (study)	3
Kalsi et al [34]	16†	Botox 200 U	–	NA/−83	−33	−68	+242	−89	–	72	4 mo (study)	3
Kalsi et al [35]	38	Botox 200 U	73 (ITT analysis)	NA/−35	−18.2	−28.1	+46	−9	–	–	4 mo (study) 10.4 mo (benefit)	3
Popat et al [13]	31†	Botox 200 U	–	57.3/NA	−36.3	−50.7	+111	−24.5	–	–	4 mo (study)	3
Smith et al [29]	17	Botox 100–300 U	50 excellent	NA/−87	−40	–	+61	0	–	–	6 mo (study)	3
Smith et al [58]	10	Botox 100 U	80	NA/NA	–	–	–	–	–	–	3–6 mo (benefit)	3
Schulte-Baukloh et al [56]	44	Botox 200–300 U	86	NA/−43	−13	–	+34	–	–	UDI−6: 28	9 mo (study) 6 mo (benefit)	3
Kessler et al [28]	11	Botox 300 U	–	91/NA	−63.6	–	+54.5	−35.5	–	–	5 mo (benefit)	3
Rajkumar et al [49]	15	Botox 300 U	–	54.5/NA	−60	–	+16.8	–	40	32	9 mo (study) 6 mo (benefit)	3
Schulte-Baukloh et al [57]	7	Botox 300 U	71.4	NA/−64	−18	–	+14	–	–	42	6 mo (study)	3
Kuo et al [50]	20	Botox 200 U	85	45/NA	–	–	+40	−28	−65	–	6 mo (study)	3
Werner et al [55]	26	Botox 100 U	60	80/NA	−35	–	+58	–	−60	–	9 mo (study)	3
Rapp et al [14]	35	Botox 300 U	58	−54 (pads: no)		–		–	–	24	6 mo (study)	3
Kuo [26]	18	Botox 200 U	78 excellent or improved	39/NA	–	–	+11*	−35*	–	51*	5.3 mo (benefit)	3
Flynn et al [48]	7	Botox 150 U	64	NA/NA	−12	–	–	–	–	77	6 mo	3
Mean			69	58/−65	−35.5	−49.9	+65.5	−32.4	54.1	47.9	6.2 mo (benefit)	–

Despite heterogeneous designs, all single-injection studies showed significant improvements in a variety of outcomes concerning symptomatology, urodynamics, and QoL. The LoE for a beneficial effect of BoNTA in idiopathic DO (IDO) is at 1b.

MCC = maximum cystometric capacity; $Pdet_{max}$ = maximum detrusor pressure; DO = detrusor overactivity; QoL = quality of life; LoE = levels of evidence; NA = not applicable; suburo = suburothelium; UDI-6 = Urinary Distress Inventory short form; ITT = intent to treat.

* Results not analysed separately for IDO or NDO and not included in analysis of means.

† Patients included in Kalsi et al [35].

effect of two different Botox dosages for this indication. Two additional, nonpivotal studies are part of this clinical development programme. These studies are being conducted to support regulatory approval for neurogenic OAB.

3.3.2. *Adult non-neurogenic overactive bladder and detrusor overactivity*

A total of 641 non-neurogenic OAB patients with or without DO demonstrable by urodynamics have been treated with BoNTs in 29 single-injection studies. These included 2 small RCTs, 1 with BoNTA and 1 with BoNTB [43,44]; 3 randomised trials comparing the efficacy or tolerance of different doses of BoNTA or the efficacy of different injection techniques with the same toxin dose [45–47]; and 23 open-label studies examining the effect of BoNTA (21 studies) [13–15,25,26,28,29,34,35,40,48–59] or BoNTB (2 studies) [60,61] on the symptoms, urodynamic parameters, and QoL of a non-neurogenic OAB/DO population alone or in comparison with results of an NDO population. The studies lack homogeneity in design and primary outcome but consistently show significant improvements in treatment parameters (Tables 5 and 6).

Summarised results showed that Botox 200 U was most commonly used in these studies. Most of the data come from intradetrusor injections. There is LoE 1b for a beneficial effect of BoNTA on OAB symptoms, urodynamic parameters, and QoL in patients with IDO refractory to oral pharmacotherapy [44]. Efficacy rates for BoNTA varied (range: 36.4–89.0%; mean: 69%) due to different definitions of efficacy and assessment tools used. Complete continence was achieved in a mean of 58% of patients (range: 32–86%); all studies reported significant reductions in incontinence episodes (mean: 65%). The mean benefit from a single treatment was 6 mo (range: 4–10 mo). The range of duration of effect depended on the dosage, site, and depth of injections (LoE 2b). There is no full paper on the efficacy of repeat injections in non-neurogenic OAB/DO. There is LoE 1b that BoNTB is also effective but of short duration [43] (Table 6).

3.4. *Comparison of different injection techniques*

Injection techniques into the bladder have not been standardised. In the original application in NDO, BoNTA was administered through a rigid cystoscope [2]. Less invasive techniques have since been introduced [25,26]. The ''Dasgupta technique'' uses ultrafine injection needles via a flexible cystoscope under local anaesthesia with injections evenly distributed in the bladder wall, apart from the

Table 6 – Studies using botulinum neurotoxin type B (BoNTB) for treatment of intractable symptoms of non-neurogenic overactive bladder (OAB) or detrusor overactivity (DO)[a]

Author	No. of patients	BoNT type, dosage	% improvement or success	Continence change, %	Frequency change, %	Urgency change, %	MCC change, %	$Pdet_{max}$	DO	QOL change, %	Duration of study or benefit	LoE
Hirst et al [61]	20	BTX/B 5000 U	62 <10 wk 35 10 wk	−50	−8.3	–	+40.7	–	–	+18.2	4.5 mo (benefit)	3
Ghei et al[a] [43]	17	BTX/B 5000 U	–	−89	−33	–	–	–	–	–	6 wk (study)	1b
Dykstra et al [60]	15	Myobloc 2500 U, Myobloc 3750 U, Myobloc 5000 U, Myobloc 10 000 U, and Myobloc 15 000 U	93	93 continent	−50	–	–	–	–	–	3 mo (benefit); longer duration with higher doses	3

MCC = maximum cystometric capacity; $Pdet_{max}$ = maximum detrusor pressure; QoL = quality of life; LoE = levels of evidence.
[a] There is high LoE of 1b that BoNTB is effective but of short duration.

trigone. It is quick and has good patient tolerability (LoE 3) [13,25].

3.4.1. *Rigid versus flexible cystoscope*

Administration of BoNTA using either a flexible or a rigid cystoscope produced significant improvements of symptoms, urodynamics, and QoL parameters in placebo-controlled and open-label studies [12,13,44], but there has been no direct comparative study. Researchers using the minimally invasive technique to inject the bladder base and trigone only claimed efficacy comparable with their older rigid cystoscopic technique (LoE 4) [58]. To prevent backflow of the toxin, either the bladder should be relatively full when rigid cystoscopic injections are performed [62], or ultrafine needles should be used [63] (LoE 4).

3.4.2. *Trigonal versus nontrigonal injections*

Based on mounting evidence that BoNTA may also affect sensory nerves, investigators have advocated injecting the trigone or the suburothelial space [13,26,50,64]. No evidence of new or worsening of preexisting vesicoureteric reflux (VUR) was found following trigonal injections [54].

3.4.3. *Number of injection sites*

No direct comparative studies exist. More extensive coverage of the toxin in the bladder was associated with better outcomes and duration of effect but at the cost of voiding dysfunction [46] (LoE 2b). Efficacy of 10-site submucosal injections was thought to be similar to that of previous work by the same group injecting 30 sites [58] (LoE 4).

The number of injection sites also depends on the dilution and dose used. The results which established the efficacy of Botox in NDO used Botox 10 U/ml per site.

Combined detrusor and sphincter injections could be used to circumvent CISC (LoE 3) [33,56,65,66].

3.4.4. *Detrusor versus suburothelial injections*

Most of the data come from detrusor injections of Botox. The LoE of data relating to the advantages of detrusor injections is 2b–4. Intradetrusor and suburothelial injections increased cystometric capacity compared with bladder-base injections (LoE 2b).

3.5. *Detrusor overactivity in children*

BoNT detrusor injections have been used in 148 children with NDO mainly due to myelomeningocele in eight open-label studies [67–74] and in one study with 21 children with non-neurogenic DO (Table 7) [75]. Indications for BoNT treatment were identical to those for adults. There has been little experience with children <3 yr old [69–71]. Published experience has been only with BoNTA, the majority of studies ($n = 5$) using Botox.

In NDO, Botox was used in dosages of 5–12 U/kg of body weight up to 300 U [67,68,70,72]; Dysport was used in dosages of 20 U/kg of body weight up to 400 U [71]. Lower dosages (Botox 100 U) were used in non-neurogenic DO [75]. Caution needs to be raised, however, regarding the total dosage in children also treated with BoNTA for spasticity. Results suggest that 11–20 injection sites would be sufficient. The choice between general anaesthesia [68,69,73] and sedoanalgesia with or without local anaesthesia [70,71] depended mainly on the age of the patient. Considerable improvements in urinary continence, MCC, $Pdet_{max}$, bladder compliance, and incidence of urinary tract infections (UTIs) were reported as well as resolution of VUR, but the LoE was only 3 (Table 7). Repeat injections at intervals of 6–9 mo led to continuous improvement [70–72], but adverse effects on detrusor compliance in the long term cannot yet be excluded [70]. Side-effects were rare and similar to those reported in adults [71]. Data on the effect of the treatment on ''low-compliance bladders'' or the use of anticholinergics [68,70,74] are insufficient.

3.6. *Urethral sphincter*

External urethral sphincter injections can be performed alone [1,29,56,76–91] or in combination with detrusor injections [33,56,65,66]. A total of 640 adults and 40 children have been treated in 17 full studies (14 with adults and 3 with children) and 2 case reports (1 with adults and 1 with children) [92,93], including 2 placebo-controlled trials and 1 active comparator–controlled trial. Most of the experience has been in patients with nDSD [1,29,33,76,78–81,83,84,86–88,90]. Other applications included dysfunctional voiding, nonrelaxing urethral sphincter, idiopathic detrusor underactivity, psychologic inhibition of voiding, iatrogenic obstruction [1,56,77,82,85,86,92], and bladder-neck dyssynergia (injection into the bladder neck) [94]. Reports involved only BoNTA. Botox dosages ranged between 50 U and 200 U; the standard dose was 100 U reconstituted in 4 ml of normal saline [1,56,65,66,76,86]. One study used Dysport 150 U [87]. Transurethral, paraurethral, or transperineal administration with or without electromyogram (EMG) guidance has been used. Improvements have been reported in the following measures: urine flow, PVR, maximal urethral closure pressure, voiding

Table 7 – Studies using botulinum neurotoxin type A (BoNTA) for treatment of intractable symptoms of neurogenic and non-neurogenic overactive bladder (OAB) or detrusor overactivity (DO) in children

Study	No. of patients	BoNT type, dosage	V_{refl} change, %	$Pdet_{max}$ change, %	MCC change, %	Bladder compliance change, %	Incontinence change, %	Duration of study or benefit	LoE
Akbar et al [71]	19	Dysport 20 U/kg up to 400 U	NA	−39	+92	+166	Continent: 84	7.8–8 mo; 3 repeat injections	3
Neel et al [74]	23	12 U/kg up to 300 U (brand not mentioned)	NA	−34	−70	NA	NA	≥6 mo	3
Altaweel et al [72]	20	5 U/kg up to 300 U (brand not mentioned)	NA	−49	+56	+160	Continent: 65	8.1 mo; 1 repeat injection	3
Kajbafzadeh et al [73]	26	Botox 10 U/kg	NA	−40	+162	NA	Incontinent: −88 Continent: 73		3
Hoebeke et al [75]	21	Botox 100 U	NA	NA	+62	NA	NA	≥6 mo	3
Schulte-Baukloh et al [70]	10	Botox 12 U/kg up to 300 U	+88	−39	+72	109	NA	7.8 mo; 5 repeat injections	3
Riccabona et al [69]	15	10 U/kg up to 360 U (brand not mentioned)	+314	−46	+117	NA	Continent: 87	10.5 mo	3
Schulte-Baukloh et al [68]	20	Botox 12 U/kg up to 300 U	+85	−42	+35	+219	NA	6 mo	3
Schulte-Baukloh et al [67]	17	Botox 12 U/kg up to 300 U	+112	−33	+57	+122	Incontinent: −33	2–4 wk	3
Average	**Σ 169** **∅ 19**	**–**	**+149.7**	**–40.3**	**+80.3**	**+155.2**	**Incontinent: −61** **Continent: 77**	**7.5 mo**	**–**

Considerable improvements are shown in the following areas: urinary continence, MCC, $Pdet_{max}$, and bladder compliance as well as downgrading or disappearance of vesicoureteric reflux, but the LoE was only 3. Repeat injections were also efficacious (LoE 3).

BoNT = botulinum neurotoxin; V_{refl} = volume at first reflex detrusor contraction; $Pdet_{max}$ = maximum detrusor pressure; MCC = maximum cystometric capacity; LoE = levels of evidence; NA = not applicable.

Table 8 – Studies using botulinum neurotoxin type A (BoNTA) for urethral sphincter injections in adults and children

Study	No. of patients	BoNT type, dosage	PVR change, %	MUP/MUCP/DLPP change, %	Max void pressure change, %	Retention (catheter free)	% improvement or success	Duration of study or benefit	LoE
Adults									
Liao and Kuo [66]	200	Botox 50–100 U	≥–50	NA	NA	–50 CISC	88.5	1 mo	3
Kuo [91]	27	Botox 50–100 U	–91	NA	NA	NA	NA	>1 yr	3
Gallien et al [86]	86	Botox 100 U vs placebo (+5 mg alfuzosin b.d. in both groups)	–15.5	NA	–21	NA	NA	~4 mo	1b
Kuo [87]	30	Botox 100 U vs medical treatment	–44.4	NA	–22	NA	80	3–9 mo	2a
Smith et al [29]	68	Botox 100–200 U	–63	NA	–36	83	NA	6 mo	3
Kuo [65]	103	Botox 50–100 U	–61	–26 MUCP	–31	87	85	4 mo	3
Kuo [85]	20	Botox 50 U	–83	–24 MUCP	–31	85	90	3–4 mo	3
De Seze et al [84]	13	Botox 100 U vs 0.5 lidocaine	–60 vs –16	NA	NA	NA	NA	31% <3 mo; 46% = 3 mo; 23% >3 mo	1b
Smith et al [92]	1	Botox 100 U	NA	NA	NA	100	100	NA	3
Phelan et al [115]	21	Botox 80–100 U	–71	–	–	90	67	3–4 mo	3
Petit et al [81]	17	Dysport 150 U	–54	–21 MUP	–20	NA	53	2–3 mo	3
Gallien et al [82]	5	Botox 100 U	–13	–0.3 MUP	–7	NA	NA	3 mo	3
Wheeler et al [80]	3	Botox 100 U	NA	NA	NA	NA	66	–	3
Schurch et al [78]	24	Botox 100 U or Dysport 250 U	–13	–48 MUP	NA	NA	NA	3 mo (1 injection); 9–13 mo (repeat injection)	3
Fowler et al [77]	6	Dysport 200 U in 1 injection (5 patients) or 2 injections (1 patient)	NA	NA	NA	NA	0	–	3
Dykstra et al [76]	5	Oculinum 140–240 U	–60	–31 MUP	NA	NA	NA	2 mo	1b
Dykstra et al [1]	11	Oculinum 20–240 U	–64	–33 MUP	NA	NA	NA	50 d	3
Average	**Σ 640 ∅ 37.6**		**–56**	**–26**	**–24**	**69**	**66**	**4.64 mo**	
Children									
Petronijevic et al [90]	9	Dysport 500 U (combined with standard/behavioural urotherapy)	–64	NA	NA	NA	78	6 mo	3
Radojicic et al [89]	20	BoNTA 50 U or 100 U (brand not mentioned)	–65	NA	NA	NA	85	≥9 mo	3
Mokhless et al [88]	10	Botox 50–100 U	–77	–37 DLPP	NA	100	NA	6 mo	3
Mall et al [93]	1	Botox 40 U	–94	NA	NA	NA	NA	≥9 wk	3
Average	**Σ 40 ∅ 10**	–	**–75**	**–37**	–	**100**	**82**	**5.75 mo**	–

There is LoE 1b for an action for the use of BoNTA in detrusor-sphincter dyssynergia in adult neurogenic patients; however, the clinical significance of the results needs further evaluation.
BoNT = botulinum neurotoxin; PVR = postvoid residual; MUP = maximum urethral pressure; MUCP = maximum urethral closing pressure; DLPP = detrusor leak-point pressure; max void pressure = maximum voiding detrusor pressure; LoE = levels of evidence; CISC = clean, intermittent self-catheterisation; NA = not applicable; b.d. = twice daily.

$Pdet_{max}$, bladder capacity, frequency of spontaneous or CISC voiding, hesitancy, and QoL (LoE 1b) (Table 8). The benefit was maintained for a mean of 4.6 mo. The database on repeated sphincter injections was weak.

Sphincter injections in children are reported almost exclusively in non-neurogenic dysfunctional voiding refractory to conservative management [83]. Administration was either transurethral [88] or transperineal [90]. Botox dosages varied (50–100 U) depending on age and body weight [88,89]; Dysport was used in dosages of up to 500 U [90]. Significant improvements have been reported in Q_{max}, pelvic floor EMG, PVR, detrusor leak-point pressure, incidence of UTIs, avoidance of clean intermittent catheterisation (CIC), hydronephrosis, and incontinence, but the LoE is only 3 (Table 8). The effect is said to last up to 6 mo [88,90]. No long-term data are available.

3.7. *Bladder pain syndrome/interstitial cystitis*

To date, only five open-label studies have examined the effect of BoNTA in a total 71 patients with bladder pain syndrome/interstitial cystitis (BPS/IC) (Table 9). The studies suffer from considerable heterogeneity in diagnostic criteria of BPS/IC, symptom severity, efficacy measures, BoNTA dose and dilution, site and number of injections, safety evaluation, and duration of follow-up. The vast majority of data come from the use of Botox; a dosage of 100–200 U is most commonly used. In four of five studies, submucosal injections of the trigone were involved in an attempt to affect the afferent pathways thought to be responsible for the origin of pain; however, a small nonrandomised comparative trial claimed no additional benefit of trigonal injections (LoE 3) [95]. In four of five studies, improvements were recorded in pain scores (mean decrease: 47.5%; range: 25–79%), daytime frequency (mean decrease: 38%; range: 23–54%), nocturia (mean decrease: 46%; range: 45–47%), and MCC (mean increase, 28%; range: 24–36%), with subjective improvement reported by 69–86% of patients [3,96–98], but the LoE is only 3 (Table 9). One study reported only 20% efficacy rate [95].

Follow-up was up to 3 mo in four of five studies. Only one study reported 1-yr follow-up results of a single injection, showing that the beneficial effect of BoNTA lasts <5 mo [98]. No data exist on repeat injections.

3.7.1. *Mechanism of action*

A single human study combining intravesical BoNTA injections with hydrodistention found

Table 9 – Studies using botulinum neurotoxin type A (BoNTA) for treatment of intractable symptoms of bladder pain syndrome/interstitial cystitis (BPS/IC)

Study	No. of patients	BoNT type, dosage	Site of injection	Follow-up, months	Daytime frequency change, %	Nocturia change, %	VAS change, %	FD vol change, %	MCC change, %	LoE
Smith et al [3]	13	Dysport/Botox 100–200 U	Submucosal trigone/ bladder floor	3	44	45	79	37	36	3
Kuo [95]	10	Botox 100–200 U	Submucosal trigone	3	23	NR	25	25	28	3
Giannantoni et al [96]	14	Botox 200 U	Submucosal trigone/ bladder floor	3	54	47	34	NR	24	3
Liu and Kuo [97]	19	Botox 100–200 U	Intravesical, plus hydrodistension 2 wk later	3	30	NR	52	NR	24	3
Giannantoni et al [98]*	15	Botox 200 U	Submucosal trigone/lateral walls	12	12.5	29	6	NR	4	3

Studies were single-centre, open-label, small-sized, and heterogeneous in their design; thus, the LoE for improvements recorded in symptoms and urodynamic parameters could only be set at 3.
VAS = visual analogue scale; FD vol = volume at first desire to void; MCC = maximum cystometric capacity; LoE = level of evidence; NR = not reported.
* The 1-yr results are presented for this study.

reduced bladder-tissue levels of NGF after treatment [97].

3.8. Prostate

3.8.1. Rationale of use

The autonomic nervous system controls secretion of prostate epithelium and contraction of smooth muscle, also displaying trophic effects [99]. Adrenergic and muscarinic receptors are abundantly distributed within the prostate [100,101].

3.8.2. Mechanism of action

In animals, BoNTA prostate injections induced atrophy of the gland and glandular apoptosis [102,103], decrease of proliferative cells and α_1-adrenergic receptors with no change of androgen receptors [104], impairment of the contractile properties of the prostate [105], and reduction in the local inflammatory reaction induced by capsaicin injection [106]. Human data are inadequate.

3.8.3. Clinical studies

To date, 118 patients with benign prostatic hyperplasia (BPH)–associated lower urinary tract symptoms (LUTS) have been treated in a single-centre RCT [4] (LoE 1b), and four open-label studies have been conducted (LoE 3) (Table 10). Most patients were poor surgical candidates or inadequately responded to first-line treatment. All studies used Botox (100–200 U) delivered via transperineal, transurethral, or transrectal injection. All studies showed significant improvements in symptom scores, peak-flow rates, PVR, prostate-specific antigen (PSA), and QoL as well as decreases in prostate size (Table 10) [4,107–110]. The validity of the available data is poor due to different inclusion criteria (eg, prostate size and severity of LUTS), routes of administration, BoNTA doses, dilutions, number of injection sites, criteria for efficacy and safety, and follow-ups that were used. Interestingly, no complications were reported. No long-term data are available, and a possible effect on sexual function has not been examined.

3.9. Pelvic-floor disorders

One RCT [111], six open-label studies [112–120], and four case studies [121–124] have examined the effect of BoNTA in 87 patients suffering from pelvic-floor muscle ''spasms'' presenting as dyspareunia, dysmenorrhoea, or vestibulodynia as well as from chronic perineal pain, anorectal disorders, and other conditions, the aetiology of which remains unknown but are thought to be related to a neuropathic type of pain and are otherwise extremely difficult to treat [125].

3.9.1. Pelvic floor spasms

BoNTA was injected into the levator ani (puborectalis and pubococcygeus) muscles under conscious sedation.

One RCT, one open-label study, and two case studies produced LoE 2a–3 for a beneficial effect of Botox on dyspareunia, dysmenorrhoea, pelvic-floor pressure, sexual dysfunction, coital pain, pelvic-floor hypertonicity, and variability, which were refractory to conservative therapy [111,112].

3.9.2. Chronic perineal pain

A single case study (LoE 3) exists of BoNTA injected into the obturator internus muscle [113].

3.9.3. Anorectal disorders

BoNTA was used on anal fissures (LoE 2b) [120,126–128], faecal urgency, chronic constipation [118,129,130], Hirchsprung's disease [124], and rectal pain [114] (LoE 3).

3.9.4. Other conditions

Evidence supporting the use of BoNTA in treating pelvic-floor dysfunction unrelated to spasms [131], postpubovaginal sling retention [132], urethral stricture [133,134], prostatitis [135], and chronic pelvic pain syndrome in men [136] is preliminary (LoE 3) and deserves further evaluation.

3.10. Safety issues

3.10.1. Allergy and antibody formation towards the protein

Allergy has been described in nonurologic treatment, but antibody development is very rare (LoE 2a). In cases of complete treatment failure after repeated intradetrusor BoNTA injections, antibody production might have a causative role [137]. Increased presence of eosinophils in the suburothelium after repeat injections is of uncertain clinical significance [138].

3.10.2. Local effects

Either less [139] or no additional fibrosis [138,140] was found after one or repeat treatments in NDO or IDO bladders (LoE 2b). A shift towards a low compliance pattern was found in some NDO patients treated with a mean dosage of Dysport 750 U [42], thought to be due to wall-elasticity reduction (LoE 3). Most studies, however, show improvement of urodynamic compliance (LoE 1b–3).

Bruising and/or local small haematoma, pain at the injection site, and pelvic pain [14] can occur (LoE

Table 10 – Studies using botulinum neurotoxin type A (BoNTA) for treatment of intractable benign prostatic hyperplasia (BPH)–associated lower urinary tract symptoms (LUTS)

Study	No. of patients (n = 118)	Dose	Administration	IPSS decrease, %	Peak flow increase, %	Prostate volume decrease, %	PSA level decrease, %	PVR decrease, %	QoL improvement, %	Follow-up, months	LoE
Maria et al [4]	30	Botox 200 U	Transperineal; 50 U/ml: 2 ml each lobe	61	180	60	44	65	NR	19.6	1b
Chuang et al [107]	16	Botox 100 U	Transperineal; 50 U/2 ml: 2 ml each lobe	61	171	60	10	61	53	10	3
Kuo [108]	10	Botox 200 U	Transurethral, 200 U/20 ml: 10 sites, lateral and median	80*	152	24	NR	85	53	6	3
Chuang et al [109]	41	Botox 100 U†	Transperineal under TRUS guidance; 4 ml dilution: 2 ml each lobe	61	61	17	NR	40	64	12	3
		Botox 200 U†	Transperineal under TRUS guidance; 4 ml dilution: 2 ml each lobe	73	70	17	NR	72	56	12	3
Silva et al [110]	21	Botox 200 U	Transrectal under TRUS guidance	NR	114	23	17	NR	NR	6	3
Mean				**64**	**125**	**35**	**24**	**65**	**52**	**10.7**	–

Despite the sound scientific background of its use and the presence of one randomised controlled trial, the validity of the data showing significant improvements in symptom scores, peak flow rates, PVR, PSA, and QoL as well as decreases in prostate size was minimised by the considerable variability in study designs and the lack of long-term follow-up.

IPSS = International Prostate Symptom Score; PSA = prostate-specific antigen; PVR = postvoid residual urine volume; QoL = quality of life; LoE = level of evidence; NR = not reported; TRUS = transrectal ultrasound.

* Dysuria.

† Based on prostate size (>30 ml).

3). Reports of UTIs vary (range: 6.4–35.0% of treated cases); although not treatment-related in NDO [12], they were associated with Botox treatment in IDO (LoE 1b) [44]. Haematuria (range: 3.2–5.0%), autonomic dysreflexia, and constipation (10% with BoNTB) [43] are also reported.

3.10.3. *Effects on nontarget organs*

Paralysis of distant muscle groups was described in case reports after injection into the sphincter [76] or the detrusor [141,142] (LoE 3). Reports of muscle weakness or ''hypoasthenia'' lasting from 2 wk to 2 mo range between 2.2% and 6% of cases treated with 1000 U Dysport [37,42,71], but were also reported with 750 U (LoE 3) [31] and with 300 U Botox [142]. Other systemic side-effects include flu-like symptoms (BoNTA) [13], dry mouth (10%), and general malaise (5%) (BoNTB) [43].

In all aspects the safety seems clinically good, though a limited number of urologic studies are available for some; however, reports of subclinical EMG effects in distant muscles and subclinical changes in respiratory heart rate variation and bowel function after treatment of nonurologic cases depict the need for further studies on possible effects of urologically applied BoNTs on other autonomic organs [143,144].

The most common side-effect of bladder injections is increased PVR, which may necessitate self-catheterisation and is of special clinical significance in IDO. This side-effect is drug related [44] (LoE 1b), and its incidence appears to be dosage dependent (LoE 1b) [45]. The rates for CISC or suprapubic catheterisation are extremely variable (range: 4–45%) [13,26,28], possibly due to variable dosages used and differences regarding definitions of PVR at which CISC is needed. Combined detrusor and sphincter injections were beneficial in circumventing transient CISC [56].

There are case reports of stress urinary incontinence and nocturnal enuresis after sphincter injection in adults and children [82,89] (LoE 3).

4. Conclusions

The use of BoNTs in LUT and pelvic-floor disorders is rapidly evolving. These guidelines summarise the most recent published or accepted literature and provide recommendations for their use in clinical practice. The consensus committee recommends further collaborative and larger placebo-controlled and comparative trials to evaluate the efficacy of single and repeat injections, the duration of effect, the short- and long-term safety, the optimal dose and injection technique, the timing for repeat injection, and the cost-effectiveness of BoNTs in treating patients with urologic and pelvic-floor disorders.

Author contributions: Apostolos Apostolidis had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Apostolidis.
Acquisition of data: Apostolidis, Dasgupta, Denys, Elneil, Fowler, Giannantoni, Karsenty, Schulte-Baukloh, Schurch, Wyndaele.
Analysis and interpretation of data: Apostolidis, Dasgupta, Denys, Elneil, Fowler, Giannantoni, Karsenty, Schulte-Baukloh, Schurch, Wyndaele.
Drafting of the manuscript: Apostolidis, Dasgupta, Denys, Elneil, Fowler, Giannantoni, Karsenty, Schulte-Baukloh, Schurch, Wyndaele.
Critical revision of the manuscript for important intellectual content: Apostolidis, Dasgupta, Denys, Elneil, Fowler, Giannantoni, Karsenty, Schulte-Baukloh, Schurch, Wyndaele.
Statistical analysis: Apostolidis, Dasgupta, Denys, Elneil, Fowler, Giannantoni, Karsenty, Schulte-Baukloh, Schurch, Wyndaele.
Obtaining funding: Apostolidis.
Administrative, technical, or material support: Aristotle University of Thessaloniki Supervision: Apostolidis.
Other (specify): None.

Financial disclosures: I certify that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: A. Apostolidis is a recipient of unrestricted educational grants from Allergan Ltd and has acted as consultant for Allergan Ltd and Astellas. He is an investigator for Allergan, Pfizer, and Astellas. P. Dasgupta is a recipient of unrestricted educational grants from Allergan Ltd and has acted as consultant for Allergan Ltd. He is also an investigator for Allergan. P. Denys is a consultant and investigator for Allergan. He is also an investigator for Astellas and Ono Pharma and is a lecturer for Lilly and Medtronic. S. Elneil is a paid consultant for Medtronic. C.J. Fowler is a recipient of unrestricted educational grants from Allergan Ltd and Pfizer Inc, is a consultant for Allergan Ltd and Medtronic, and is an investigator for Allergan. A. Giannantoni is a paid consultant for Allergan (Irvine-USA). G. Karsenty is a consultant for Allergan France and Medtronic MGU. His collaboration with Allergan France consists in being part of the French study group for the use of Botox in the lower urinary tract. He organizes hands-on training sessions on Interstim therapy (Medtronic) for lower urinary tract dysfunctions. B. Schurch is a paid consultant and investigator for Allergan, Astellas, and Pfizer. J.-J. Wyndaele has acted as a consultant for Pfizer, Eli Lilly, and Novartis. He has received honoraria from Astellas, Pfizer, Novartis, Eli Lilly, and Ismar Healthcare. He has been or is an investigator for Astellas, Pfizer, GSK, Novartis, Esteril,

Allergan, and Schwarz. H. Schulte-Baukloh has no conflicts of interest.

Funding/Support and role of the sponsor: Allergan provided an unrestricted educational grant towards the realisation of the First European Consensus Conference on the use of Botulinum toxin in Urology. Pfizer, Astellas, Ipsen, and Sanofi-Aventis provided travel awards towards the Third European Masterclass on the Use of Botulinum Toxin in Urology. The abovementioned companies did not have a role in the conception and design of the events, in the collection, management, analysis, and interpretation of the data, and in the preparation, review, or approval of the manuscript. Allergan kindly provided information included in section 3.3.1, last paragraph.

References

[1] Dykstra DD, Sidi AA, Scott AB, Pagel JM, Goldish GD. Effects of botulinum A toxin on detrusor-sphincter dyssynergia in spinal cord injury patients. J Urol 1988;139:919–22.

[2] 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;164:692–7.

[3] Smith CP, Radziszewski P, Borkowski A, Somogyi GT, Boone TB, Chancellor MB. Botulinum toxin A has antinociceptive effects in treating interstitial cystitis. Urology 2004;64:871–5, discussion 875.

[4] Maria G, Brisinda G, Civello IM, Bentivoglio AR, Sganga G, Albanese A. Relief by botulinum toxin of voiding dysfunction due to benign prostatic hyperplasia: results of a randomized, placebo-controlled study. Urology 2003; 62:259–64, discussion 264–5.

[5] Sievert KD, Bremer J, Burgdörfer H, et al. Botulinum toxin for the treatment of neurogenic detrusor hyperactivity [Consensus paper on use for neurogenic bladder dysfunction]. Urologe A 2007;46:293–6.

[6] 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: 275–87.

[7] Duthie J, Wilson DI, Herbison GP, Wilson D. Botulinum toxin injections for adults with overactive bladder syndrome. Cochrane Database Syst Rev 2007;3: CD005493.

[8] US Department of Health and Human Services. Public Health Service, Agency for Health Care Policy and Research. Washington, DC: US Dept of Health and Human Services; 1992. p. 115–27.

[9] Dolly O. Synaptic transmission: inhibition of neurotransmitter release by botulinum toxins. Headache 2003;43(Suppl 1):S16–24.

[10] Brin MF. Botulinum toxin: chemistry, pharmacology, toxicity, and immunology. Muscle Nerve 1997;6(Suppl): S146–68.

[11] Reitz A, Stöhrer M, Kramer G, et al. European experience of 200 cases treated with botulinum-A toxin injections into the detrusor muscle for urinary incontinence due to neurogenic detrusor overactivity. Eur Urol 2004;45:510–5.

[12] Schurch B, de Seze M, Denys P, et al. Botulinum toxin type A is a safe and effective treatment for neurogenic urinary incontinence: results of a single treatment, randomized, placebo controlled 6-mo study. J Urol 2005;174: 196–200.

[13] Popat R, Apostolidis A, Kalsi V, Gonzales G, Fowler CJ, Dasgupta P. A comparison between the response of patients with idiopathic detrusor overactivity and neurogenic detrusor overactivity to the first intradetrusor injection of botulinum-A toxin. J Urol 2005;174:984–8.

[14] Rapp DE, Lucioni A, Katz EE, O'Connor RC, Gerber GS, Bales GT. Use of botulinum-A toxin for the treatment of refractory overactive bladder symptoms: an initial experience. Urology 2004;63:1071–5.

[15] Schmid DM, Sauermann P, Werner M, et al. Experience with 100 cases treated with botulinum-A toxin injections in the detrusor muscle for idiopathic overactive bladder syndrome refractory to anticholinergics. J Urol 2006;176: 177–85.

[16] Yoshimura N. Bladder afferent pathway and spinal cord injury: possible mechanisms inducing hyperreflexia of the urinary bladder. Prog Neurobiol 1999;57:583–606.

[17] Apostolidis A, Dasgupta P, Fowler CJ. Proposed mechanism for the efficacy of injected botulinum toxin in the treatment of human detrusor overactivity. Eur Urol 2006;49:644–50.

[18] 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;174:977–83.

[19] Giannantoni A, Di Stasi SM, Nardicchi V, et al. Botulinum-A toxin injections into the detrusor muscle decrease nerve growth factor bladder tissue levels in patients with neurogenic detrusor overactivity. J Urol 2006;175:2341–4.

[20] Andersson KE, Appel R, Cardozo L, et al. Pharmacological treatment of urinary incontinence. In: Abrams P, Cardozo L, Khoury S, Wein A, editors. Incontinence: 3rd International Consultation on Incontinence. Paris, France: Health Publication Ltd; 2005. p. 809–54.

[21] Ehren I, Volz D, Farrelly E, et al. Efficacy and impact of botulinum toxin A on quality of life in patients with neurogenic detrusor overactivity: a randomised, placebo-controlled, double-blind study. Scand J Urol Nephrol 2007;41:335–40.

[22] Giannantoni A, Di Stasi SM, Stephen RL, Bini V, Costantini E, Porena M. Intravesical resiniferatoxin versus botulinum-A toxin injections for neurogenic detrusor overactivity: a prospective randomized study. J Urol 2004; 172:240–3.

[23] Kennelly MJ, Kang J. Botulinum-A toxin injections as a treatment for refractory detrusor hyperreflexia. Top Spinal Cord Inj Rehabil 2003;8:46–53.

[24] Bagi P, Biering-Sorensen F. Botulinum toxin A for treatment of neurogenic detrusor overactivity and inconti-

nence in patients with spinal cord lesions. Scand J Urol Nephrol 2004;38:495–8.
[25] Harper M, Popat R, Dasgupta R, Fowler CJ, Dasgupta P. A minimally invasive technique for outpatient local anaesthetic administration of intradetrusor botulinum toxin in intractable detrusor overactivity. BJU Int 2003;92: 325–6.
[26] Kuo HC. Urodynamic evidence of effectiveness of botulinum A toxin injection in treatment of detrusor overactivity refractory to anticholinergic agents. Urology 2004;63:868–72.
[27] Giannantoni A, Mearini E, Di Stasi SM, et al. New therapeutic options for refractory neurogenic detrusor overactivity. Minerva Urol Nephrol 2004;56:79–87.
[28] Kessler TM, Danuser H, Schumacher M, Studer UE, Burkhard FC. Botulinum A toxin injections into the detrusor: an effective treatment in idiopathic and neurogenic detrusor overactivity? Neurourol Urodyn 2005;24: 231–6.
[29] Smith CP, Nishiguchi J, O'Leary M, Yoshimura N, Chancellor MB. Single-institution experience in 110 patients with botulinum toxin A injection into bladder or urethra. Urology 2005;65:37–41.
[30] Klaphajone J, Kitisomprayoonkul W, Sriplakit S. Botulinum toxin type A injections for treating neurogenic detrusor overactivity combined with low-compliance bladder in patients with spinal cord lesions. Arch Phys Med Rehabil 2005;86:2114–8.
[31] Grosse J, Kramer G, Stöhrer M. Success of repeat detrusor injections of botulinum A toxin in patients with severe neurogenic detrusor overactivity and incontinence. Eur Urol 2005;47:653–9.
[32] Hajebrahimi S, Altaweel W, Cadoret J, Cohen E, Corcos J. Efficacy of botulinum-A toxin in adults with neurogenic overactive bladder: initial results. Can J Urol 2005; 12:2543–6.
[33] Schulte-Baukloh H, Schobert J, Stolze T, Sturzebecher B, Weiss C, Knispel HH. Efficacy of botulinum-A toxin bladder injections for the treatment of neurogenic detrusor overactivity in multiple sclerosis patients: an objective and subjective analysis. Neurourol Urodyn 2006;25:110–5.
[34] 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;49:528–35.
[35] Kalsi V, Popat RB, Apostolidis A, et al. Cost-consequence analysis evaluating the use of botulinum neurotoxin-A in patients with detrusor overactivity based on clinical outcomes observed at a single UK centre. Eur Urol 2006; 49:519–27.
[36] Kuo HC. Therapeutic effects of suburothelial injection of botulinum a toxin for neurogenic detrusor overactivity due to chronic cerebrovascular accident and spinal cord lesions. Urology 2006;67:232–6.
[37] 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;97:1030–4.
[38] 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;68:1193–7.
[39] Kalsi V, Gonzales G, Popat R, et al. Botulinum injections for the treatment of bladder symptoms of multiple sclerosis. Ann Neurol 2007;62:452–7.
[40] Kalsi V, Apostolidis A, Gonzales G, Elneil S, Dasgupta P, Fowler CJ. Early effect on the overactive bladder symptoms following botulinum neurotoxin type A injections for detrusor overactivity. Eur Urol 2008;54:181–7.
[41] Reitz A, Denys P, Fermanian C, Schurch B, Comperat E, Chartier-Kastler E. Do repeat intradetrusor botulinum toxin type A injections yield valuable results? Clinical and urodynamic results after five injections in patients with neurogenic detrusor overactivity. Eur Urol 2007; 52:1729–35.
[42] Del Popolo G, Filocamo MT, Li Marzi V, et al. Neurogenic detrusor overactivity treated with English botulinum toxin A: 8-year experience of one single centre. Eur Urol 2008;53:1013–20.
[43] 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;174:1873–7, discussion 1877.
[44] Sahai A, Khan MS, Dasgupta P. Efficacy of botulinum toxin-A for treating idiopathic detrusor overactivity: results from a single center, randomized, double-blind, placebo-controlled trial. J Urol 2007;177:2231–6.
[45] Kuo HC. Will suburothelial injection of small dose of botulinum A toxin have similar therapeutic effects and less adverse events for refractory detrusor overactivity? Urology 2006;68:993–7, discussion 997–8.
[46] Kuo HC. Comparison of effectiveness of detrusor, suburothelial and bladder base injections of botulinum toxin a for idiopathic detrusor overactivity. J Urol 2007;178:1359–63.
[47] Cohen BL, Rivera R, Barboglio P, Gousse A. Safety and tolerability of sedation-free flexible cystoscopy for intradetrusor botulinum toxin A injection. J Urol 2007;177: 1006–10.
[48] Flynn MK, Webster GD, Amundsen CL. The effect of botulinum-A toxin on patients with severe urge urinary incontinence. J Urol 2004;172:2316–20.
[49] Rajkumar GN, Small DR, Mustafa AW, Conn G. A prospective study to evaluate the safety, tolerability, efficacy and durability of response of intravesical injection of botulinum toxin type A into detrusor muscle in patients with refractory idiopathic detrusor overactivity. BJU Int 2005;96:848–52.
[50] Kuo HC. Clinical effects of suburothelial injection of botulinum A toxin on patients with nonneurogenic detrusor overactivity refractory to anticholinergics. Urology 2005;66:94–8.
[51] Lucioni A, Rapp DE, Gong EM, Fedunok P, Bales GT. Intravesical botulinum type A toxin injection in patients

with overactive bladder: Trigone versus trigone-sparing injection. Can J Urol 2006;13:3291–5.
[52] Lee JC, Yokoyama T, Hwang HJ, et al. Clinical application of Clostridium botulinum type A neurotoxin purified by a simple procedure for patients with urinary incontinence caused by refractory destrusor overactivity. FEMS Immunol Med Microbiol 2007;51:201–11.
[53] Ghalayini IF, Al-Ghazo MA. Intradetrusor injection of botulinum-A toxin in patients with idiopathic and neurogenic detrusor overactivity: urodynamic outcome and patient satisfaction. Neurourol Urodyn 2007;26:531–6.
[54] Karsenty G, Elzayat E, Delapparent T, St-Denis B, Lemieux MC, Corcos J. Botulinum toxin type a injections into the trigone to treat idiopathic overactive bladder do not induce vesicoureteral reflux. J Urol 2007;177:1011–4.
[55] Werner M, Schmid DM, Schüssler B. Efficacy of botulinum-A toxin in the treatment of detrusor overactivity incontinence: a prospective nonrandomized study. Am J Obstet Gynecol 2005;192:1735–40.
[56] Schulte-Baukloh H, Weiss C, Stolze T, et al. Botulinum-A toxin detrusor and sphincter injection in treatment of overactive bladder syndrome: objective outcome and patient satisfaction. Eur Urol 2005;48:984–90, discussion 990.
[57] Schulte-Baukloh H, Weiss C, Stolze T, Sturzebecher B, Knispel HH. Botulinum-A toxin for treatment of overactive bladder without detrusor overactivity: urodynamic outcome and patient satisfaction. Urology 2005;66:82–7.
[58] Smith CP, Chancellor MB. Simplified bladder botulinum-toxin delivery technique using flexible cystoscope and 10 sites of injection. J Endourol 2005;19:880–2.
[59] Jeffery S, Fynes M, Lee F, Wang K, Williams L, Morley R. Efficacy and complications of intradetrusor injection with botulinum toxin A in patients with refractory idiopathic detrusor overactivity. BJU Int 2007;100:1302–6.
[60] 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;14:424–6.
[61] Hirst GR, Watkins AJ, Guerrero K, et al. Botulinum toxin B is not an effective treatment of refractory overactive bladder. Urology 2007;69:69–73.
[62] Schulte-Baukloh H, Knispel HH. A minimally invasive technique for outpatient local anaesthetic administration of intradetrusor botulinum toxin in intractable detrusor overactivity. BJU Int 2005;95:454.
[63] Apostolidis A, Dasgupta R, Fowler CJ, Dasgupta P. A minimally invasive technique for outpatient local anaesthetic administration of intradetrusor botulinum toxin in intractable detrusor overactivity. BJU Int 2005;96:917–8.
[64] Kuo HC. Preliminary results of suburothelial injection of botulinum a toxin in the treatment of chronic interstitial cystitis. Urol Int 2005;75:170–4.
[65] Kuo HC, Botulinum. A toxin urethral injection for the treatment of lower urinary tract dysfunction. J Urol 2003;170:1908–12.
[66] Liao YM, Kuo HC. Causes of failed urethral botulinum toxin A treatment for emptying failure. Urology 2007;70:763–6.
[67] Schulte-Baukloh H, Michael T, Schobert J, Stolze T, Knispel HH. Efficacy of botulinum-a toxin in children with detrusor hyperreflexia due to myelomeningocele: preliminary results. Urology 2002;59:325–7, discussion 327–8.
[68] Schulte-Baukloh H, Michael T, Stürzebecher B, Knispel HH. Botulinum-A toxin detrusor injection as a novel approach in the treatment of bladder spasticity in children with neurogenic bladder. Eur Urol 2003;44:139–43.
[69] Riccabona M, Koen M, Schindler M, et al. Botulinum-A toxin injection into the detrusor: a safe alternative in the treatment of children with myelomeningocele with detrusor hyperreflexia. J Urol 2004;171:845–8, discussion 848.
[70] Schulte-Baukloh H, Knispel HH, Stolze T, Weiss C, Michael T, Miller K. Repeated botulinum-A toxin injections in treatment of children with neurogenic detrusor overactivity. Urology 2005;66:865–70, discussion 870.
[71] 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;100:639–45.
[72] Altaweel W, Jednack R, Bilodeau C, Corcos J. Repeated intradetrusor botulinum toxin type A in children with neurogenic bladder due to myelomeningocele. J Urol 2006;175:1102–5.
[73] Kajbafzadeh AM, Moosavi S, Tajik P, et al. Intravesical injection of botulinum toxin type A: management of neuropathic bladder and bowel dysfunction in children with myelomeningocele. Urology 2006;68:1091–6.
[74] Neel KF, Soliman S, Salem M, Seida M, Al-Hazmi H, Khatab A. Botulinum-A toxin: solo treatment for neuropathic noncompliant bladder. J Urol 2007;78:2593–7.
[75] Hoebeke P, De Caestecker K, Vande Walle J, et al. The effect of botulinum-A toxin in incontinent children with therapy resistant overactive detrusor. J Urol 2006;176:328–30, discussion 330–1.
[76] Dykstra DD, Sidi AA. Treatment of detrusor-sphincter dyssynergia with botulinum A toxin: a double-blind study. Arch Phys Med Rehabil 1990;71:24–6.
[77] Fowler CJ, Betts CD, Christmas TJ, Swash M, Fowler CG. Botulinum toxin in the treatment of chronic urinary retention in women. Br J Urol 1992;70:387–9.
[78] 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;155:1023–9.
[79] Schurch B, Hodler J, Rodic B. Botulinum A toxin as a treatment of detrusor-sphincter dyssynergia in patients with spinal cord injury: MRI-controlled transperineal injections. J Neurol Neurosurg Psychiatry 1997;63:474–6.
[80] Wheeler JSJ, Walter JS, Chintam RS, Rao S. Botulinum toxin injections for voiding dysfunction following SCI. J Spinal Cord Med 1998;21:227–9.
[81] Petit H, Wiart L, Gaujard E, et al. Botulinum A toxin treatment for detrusor-sphincter dyssynergia in spinal cord disease. Spinal Cord 1998;36:91–4.
[82] Gallien P, Robineau S, Verin M, Le Bot MP, Nicolas B, Brissot R. Treatment of detrusor sphincter dyssynergia

by transperineal injection of botulinum toxin. Arch Phys Med Rehabil 1998;79:715–7.
[83] Homsey Y, Austin P. Dysfunctional voiding disorders and nocturnal enuresis. In: Belmann AB, King LR, Kraner SA, editors. Clinical pediatric urology 2002. London, UK: Martin Duntiz; 2002. p. 345–70.
[84] de Sèze M, Petit H, Gallien P, et al. Botulinum A toxin and detrusor sphincter dyssynergia: a double-blind lidocaine-controlled study in 13 patients with spinal cord disease. Eur Urol 2002;42:56–62.
[85] Kuo HC. Effect of botulinum A toxin in the treatment of voiding dysfunction due to detrusor underactivity. Urology 2003;61:550–4.
[86] Gallien P, Reymann JM, Amarenco G, Nicolas B, de Seze M, Bellissant E. Placebo-controlled, randomised, double-blind study of the effects of botulinum A toxin on detrusor sphincter dyssynergia in multiple sclerosis patients. J Neurol Neurosurg Psychiatry 2005;76:1670–6.
[87] Kuo HC. Effectiveness of urethral injection of botulinum A toxin in the treatment of voiding dysfunction after radical hysterectomy. Urol Int 2005;75:247–51.
[88] Mokhless I, Gaafar S, Fouda K, Shafik M, Assem A. Botulinum A toxin urethral sphincter injection in children with nonneurogenic neurogenic bladder. J Urol 2006;176:1767–70, discussion 1770.
[89] Radojicic ZI, Perovic SV, Milic NM. Is it reasonable to treat refractory voiding dysfunction in children with botulinum-A toxin? J Urol 2006;176:332–6, discussion 336.
[90] Petronijevic V, Lazovic M, Vlajkovic M, Slavkovic A, Golubovic E, Miljkovic P. Botulinum toxin type A in combination with standard urotherapy for children with dysfunctional voiding. J Urol 2007;178:2599–602, discussion 2602–3.
[91] Kuo HC. Recovery of detrusor function after urethral botulinum A toxin injection in patients with idiopathic low detrusor contractility and voiding dysfunction. Urology 2007;69:57–61, discussion 61–62.
[92] Smith CP, O'Leary M, Erickson J, Somogyi GT, Chancellor MB. Botulinum toxin urethral sphincter injection resolves urinary retention after pubovaginal sling operation. Int Urogynecol J Pelvic Floor Dysfunct 2002;13:55–6.
[93] Mall V, Glocker FX, Frankenschmidt A, et al. Treatment of neuropathic bladder using botulinum toxin A in a 1-yr-old child with myelomeningocele. Pediatr Nephrol 2001;16:1161–2.
[94] Lim SK, Quek PLC. Intraprostatic and bladder-neck injection of botulinum A toxin in treatment of males with bladder-neck dyssynergia: a pilot study. Eur Urol 2008; 53:620–7.
[95] Kuo H. Preliminary results of suburothelial injection of botulinum A toxin in the treatment of chronic interstitial cystitis. Urologia Internationalis 2005;75:170–4.
[96] Giannantoni A, Costantini E, Di Stasi SM, Tascini MC, Bini V, Porena M. Botulinum A toxin intravesical injections in the treatment of painful bladder syndrome: a pilot study. Eur Urol 2006;49:704–9.
[97] Liu HT, Kuo HC. Intravesical botulinum toxin A injections plus hydrodistension can reduce nerve growth factor production and control bladder pain in interstitial cystitis. Urology 2007;70:463–8.
[98] Giannantoni A, Porena M, Costantini E, Zucchi A, Mearini L, Mearini E. Botulinum A toxin intravesical injection in patients with painful bladder syndrome: 1-yr follow-up. J Urol 2008;179:1031–4.
[99] McVary KT, McKenna KE, Lee C. Prostate innervation. Prostate 1998;8(Suppl):2–13.
[100] Witte LPW, Chapple CR, de la Rosette JJMCH, Michel MC. Cholinergic innervation and muscarinic receptors in the human prostate. Eur Urol 2008;54:326–34.
[101] Pennefather JN, Lau WA, Mitchelson F, Ventura S. The autonomic and sensory innervation of the smooth muscle of the prostate gland: a review of pharmacological and histological studies. J Auton Pharmacol 2000;20:193–206.
[102] Doggweiler R, Zermann DH, Ishigooka M, Schmidt RA. Botox-induced prostatic involution. Prostate 1998;37:44–50.
[103] Chuang YC, Tu CH, Huang CC, et al. Intraprostatic injection of botulinum toxin type-A relieves bladder outlet obstruction in human and induces prostate apoptosis in dogs. BMC Urol 2006;6:12.
[104] Chuang YC, Huang CC, Kang HY, et al. Novel action of botulinum toxin on the stromal and epithelial components of the prostate gland. J Urol 2006;175:1158–63.
[105] Lin ATL, Yang AH, Chen K-K. Effects of botulinum toxin A on the contractile function of dog prostate. Eur Urol 2007;52:582–9.
[106] Chuang Y-C, Yoshimura N, Wu M, et al. Intraprostatic capsaicin injection as a novel model for nonbacterial prostatitis and effects of botulinum toxin A. Eur Urol 2007;51:1119–27.
[107] Chuang YC, Chiang PH, Huang CC, Yoshimura N, Chancellor MB. Botulinum toxin type A improves benign prostatic hyperplasia symptoms in patients with small prostates. Urology 2005;66:775–9.
[108] Kuo HC. Prostate botulinum A toxin injection—an alternative treatment for benign prostatic obstruction in poor surgical candidates. Urology 2005;65:670–4.
[109] Chuang YC, Chiang PH, Yoshimura N, De Miguel F, Chancellor MB. Sustained beneficial effects of intraprostatic botulinum toxin type A on lower urinary tract symptoms and quality of life in men with benign prostatic hyperplasia. BJU Int 2006;98:1033–7, discussion 1337.
[110] Silva J, Silva C, Saraiva L, et al. Intraprostatic botulinum toxin type A injection in patients unfit for surgery presenting with refractory urinary retention and benign prostatic enlargement. Effect on prostate volume and micturition resumption. Eur Urol 2008;53:153–9.
[111] Abbott JA, Jarvis SK, Lyons SD, Thomson A, Vancaille TG. Botulinum toxin type A for chronic pain and pelvic floor spasm in women: a randomized controlled trial. Obstet Gynecol 2006;108:915–23.
[112] Brown CS, Glazer HI, Vogt V, Menkes D, Bachmann G. Subjective and objective outcomes of botulinum toxin type A treatment in vestibulodynia: pilot data. J Reprod Med 2006;51:635–41.
[113] Gajraj NM. Botulinum toxin a injection of the obturator internus muscle for chronic perineal pain. J Pain 2005;6:333–7.

[114] Jarvis SK, Abbott JA, Lenart MB, Steensma A, Vancaillie TG. Pilot study of botulinum toxin type A in the treatment of chronic pelvic pain associated with spasm of the levator ani muscles. Aust N Z J Obstet Gynaecol 2004;44:46–50.
[115] Phelan MW, Franks M, Somogyi GT, et al. Botulinum toxin urethral sphincter injection to restore bladder emptying in men and women with voiding dysfunction. J Urol 2001;165:1107–10.
[116] Zermann D-H, Ishigooka M, Schubert J, Schmidt RA. Perisphincteric injection of botulinum toxin type A: a treatment option for patients with chronic prostatic pain? Eur Urol 2000;38:393–9.
[117] Christiansen J, Bruun E, Skjoldbye B, Hagen K. Chronic idiopathic anal pain: analysis of ultrasonography, pathology, and treatment. Dis Colon Rectum 2001;44:661–5.
[118] Maria G, Brisinda G, Bentivoglio AR, Cassetta E, Albanese A. Botulinum toxin in the treatment of outlet obstruction constipation caused by puborectalis syndrome. Dis Colon Rectum 2000;43:376–80.
[119] Pascual M, Courtier R, Gil MJ, et al. Endosonographic and manometric assessment of the internal anal sphincter in patients with chronic anal fissure. Cir Esp 2005;77:27–30.
[120] Tranqui P, Trottier DC, Victor C, Freeman JB. Nonsurgical treatment of chronic anal fissure: nitroglycerin and dilatation versus nifedipine and botulinum toxin. Can J Surg 2006;49:41–5.
[121] Gunter J, Brewer A, Tawfik O. Botulinum toxin A for vulvodynia: a case report. J Pain 2004;5:238–40.
[122] Thomson AJ, Jarvis SK, Lenart M, Abbott JA, Vancaillie TG. The use of botulinum toxin type A (Botox) as treatment for intractable chronic pelvic pain associated with spasm of the levator ani muscles. Br J Obstet Gynaecol 2005;112:247–9.
[123] Jost WH, Schanne S, Mlitz H, Schimrigk K. Perianal thrombosis following injection therapy into the external anal sphincter using botulin toxin. Dis Colon Rectum 1995;38:781.
[124] Langer JC, Birnbaum E. Preliminary experience with intrasphincteric botulinum toxin for persistent constipation after pull-through for Hirschsprung's disease. J Pediatr Surg 1997;32:1059–61, discussion 1061–2.
[125] Fritsch H, Lienemann A, Brenner E, Ludwikowski B. Clinical anatomy of the pelvic floor. Adv Anat Embryol Cell Biol 2004;175:III–X, 1–64.
[126] Gui D, Cassetta E, Anastasio G, Bentivoglio AR, Maria G, Albanese A. Botulinum toxin for chronic anal fissure. Lancet 1994;344:1127–8.
[127] Nelson R. Nonsurgical therapy for anal fissure. Cochrane Database Syst Rev 2003;4:CD003431.
[128] Nelson R. Nonsurgical therapy for anal fissure. Cochrane Database Syst Rev 2006;4:CD003431.
[129] Bosshard W, Dreher R, Schnegg JF, Bula CJ. The treatment of chronic constipation in elderly people: an update. Drugs Aging 2004;21:911–30.
[130] Baig MK, Boyer ML, Marquez H, Wexner SD. Alleviating debilitating, chronic constipation with colostomy after appendicostomy: a case study. Ostomy Wound Manage 2005;51:60–3.
[131] Langford CF, Udvari Nagy S, Ghoniem GM. Levator ani trigger point injections: an underutilized treatment for chronic pelvic pain. Neurourol Urodyn 2007;26:59–62.
[132] Lai HH, Smith CP. Hitting below the belt (bladder): botulinum treatment of urethral and prostate disorders. Curr Urol Rep 2007;8:351–8.
[133] Mazo EB, Krivoborodov GG, Shkolnikov ME. Botulinic toxin in patients with neurogenic dysfunction of the lower urinary tracts. Urologia 2004;4:44–8.
[134] Khera M, Boone TB, Smith CP. Botulinum toxin type A: a novel approach to the treatment of recurrent urethral strictures. J Urol 2004;172:574–5.
[135] El-Hakim A. Chronic prostatitis/chronic pelvic pain syndrome: Is there a role for local drug infiltration therapy? J Endourol 2004;18:227–31.
[136] Zermann DH, Ishigooka M, Doggweiler-Wiygul R, Schubert J, Schmidt RA. The male chronic pelvic pain syndrome. World J Urol 2001;19:173–9.
[137] Schulte-Baukloh H, Bigalke H, Heine G, et al. Antibodies against botulinum neurotoxin type A as a cause of treatment failure after the first detrusor injection. Urology 2007;69:575, e13–5.
[138] Apostolidis A, Jacques TS, Freeman A, et al. Histological changes in the urothelium and suburothelium of human overactive bladder following intradetrusor injections of botulinum neurotoxin type A for the treatment of neurogenic or idiopathic detrusor overactivity. Eur Urol 2008;53:1245–53.
[139] Compérat E, Reitz A, Delcourt A, Capron F, Denys P, Chartier-Kastler E. Histologic features in the urinary bladder wall affected from neurogenic overactivity—a comparison of inflammation, oedema and fibrosis with and without injection of botulinum toxin type A. Eur Urol 2006;50:1058–64.
[140] Haferkamp A, Schurch B, Reitz A, et al. Lack of ultrastructural detrusor changes following endoscopic injection of botulinum toxin type A in overactive neurogenic bladder. Eur Urol 2004;46:784–91.
[141] Wyndaele JJ, van Dromme SA. Muscular weakness as side effect of botulinum toxin injection for neurogenic detrusor overactivity. Spinal Cord 2002;40:599–600.
[142] De Laet K, Wyndaele JJ. Adverse events after botulinum A toxin injection for neurogenic voiding disorders. Spinal Cord 2005;43:397–9.
[143] Girlanda P, Vita G, Nicolosi C, Milone S, Messina C. Botulinum toxin therapy: distant effects on neuromuscular transmission and autonomic nervous system. J Neurol Neurosurg Psychiatry 1992;55:844–5.
[144] Dutton JJ. Botulinum-A toxin in the treatment of craniocervical muscle spasms: short- and long-term, local and systemic effects. Surv Ophthalmol 1996;41:51–65.

Editorial Comment on: Recommendations on the Use of Botulinum Toxin in the Treatment of Lower Urinary Tract Disorders and Pelvic Floor Dysfunctions: A European Consensus Report

Christopher Chapple
Royal Hallamshire Hospital, Sheffield, UK
c.r.chapple@shef.ac.uk

The authors are to be congratulated on this endeavour, which for the first time has provided an evidence-based literature review using the European Association of Urology (EAU) levels of evidence [1]. The review covers all of the current potential applications of botulinum toxin therapy attributed to lower urinary tract and pelvic floor dysfunction. Inevitably, one of the problems is that much of the current literature is based on small case series and there is little in the way of adequately powered controlled studies, although such studies are currently being conducted.

A caveat that needs to be borne in mind when considering use of any type of botulinum toxin product is that different preparations are not interchangeable. This caveat refers not only to dosing recommendations but also to efficacy and safety data of a particular brand. To date, the majority of data published have used the botulinum toxin A preparation from Allergan. The vast majority of published data are derived from experience in the adult population and not the paediatric population; hence, extrapolation between different age groups cannot be carried out safely until further data are available.

Based on the evidence available, the authors are able to provide a grade A level of recommendation for botulinum toxin type A for the treatment of the intractable symptoms of neurogenic detrusor overactivity (NDO) or idiopathic detrusor overactivity (IDO). They recommend caution in the context of IDO.

We should recognise that, at present, this therapy is clearly effective for NDO and IDO and is being used on a named patient basis, and it is important that this is emphasised to patients. Regulatory trials are currently under way, and it will be interesting to see the outcome of those. There are certainly a number of other aspects which need to be investigated in the future, including the most effective dose in different clinical conditions and the site and depth of injection. Clearly, we also need longer term information relating to the consequence of chronic use of the therapy, both in terms of ultrastructural changes in the bladder and neural innervation.

Reference

[1] 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;55:100–20.

DOI: 10.1016/j.eururo.2008.09.041

DOI of original article: 10.1016/j.eururo.2008.09.009