Review Article

Use of botulinum toxin for voiding dysfunction

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Abstract: The use of botulinum toxin A (BoNT-A) has expanded across a range of lower urinary tract conditions. This review provides an overview of the current indications for BoNT-A in the lower urinary tract and critically evaluates the published evidence within each area. The classic application of BoNT-A has been in the management of refractory neurogenic detrusor overactivity (NDO) and overactive bladder (OAB). There is a large volume of high-quality evidence, including numerous randomized placebo-controlled trials, which demonstrate the efficacy of BoNT-A over a long follow-up period. The culmination of this robust evidence-base has led to onabotulinumtoxin A (onaBoNT-A) receiving regulatory approval as a second-line treatment for NDO at a dose of 200 U and OAB at dose of 100 U. Other applications for BoNT-A are used on an off-license basis and include interstitial cystitis/bladder pain syndrome (IC/BPS), benign prostatic hyperplasia (BPH), and detrusor sphincter dyssynergia (DSD). These applications are associated with a less mature evidence-base although the literature is rapidly evolving. At present, the results for painful bladder syndrome (PBS) are promising and BoNT-A injections are recommended as a fourth line option in recent international guidelines, although larger randomized study with longer follow-up are required to confirm the initial findings. As a treatment for DSD, BoNT-A injections have shown potential but only in a small number of trials of limited quality. No definite recommendation can be made based on the current evidence. Finally, the results for the treatment of BPH have been variable and recent high quality randomized controlled trials (RCTs) have suggested no benefit over placebo so at present it cannot be recommended for routine clinical practice. Future advances of BoNT-A include liposome encapsulated formulations which are being developed as an alternative to intravesical injections.

Keywords: Botulinum toxin A (BoNT-A); detrusor overactivity (DO); overactive bladder (OAB); painful bladder syndrome (PBS); interstitial cystitis (IC); benign prostatic hyperplasia (BPH)

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Introduction

The use of botulinum toxin A (BoNT-A) for the treatment of lower urinary tract conditions has rapidly expanded over the last two decades. At present, BoNT-A has become a well-established therapy in the management of neurogenic detrusor overactivity (NDO) and idiopathic overactive bladder (OAB). Although these are the only licensed indications within the urinary tract, there are a wide range of off-license indications including bladder pain syndrome (BPS), detrusor sphincter dyssynergia (DSD) and benign prostatic hyperplasia (BPH).

Botulinum toxin (BoNT) was first isolated and purified as crystalline product in 1946 (1) and was initially used to treat ocular strabismus in 1977 (2). Subsequently, the treatment spread to a broad range of conditions associated with muscular hyperactivity, glandular hypersecretion and inflammation (3). The initial use within the urinary tract was

described in 1988 by Dykstra *et al.* who injected BoNT-A into the external urethral sphincter to treat DSD in patients with spinal cord injury (SCI) (4). This remained the single application until Schurch *et al.* published a landmark paper on intravesical BoNT-A injections for NDO (5). This was followed by a rapid expansion in the application of BoNT-A across idiopathic detrusor overactivity (IDO) (6,7), BPS (8) and BPH (9).

As the range of applications for BoNT-A continues to expand, this article reviews the current evidence for the most common indications for BoNT-A in the lower urinary tract. The review focuses on BoNT-A injections in adults with NDO, OAB, PBS/IC or BPH. The most recent published literature is critically evaluated and we summarize the mechanism of action, injection technique, efficacy and adverse events (AEs) for each indication.

Types of BoNT

BoNT is a potent neurotoxin synthesized by the gram positive, aerobic spore-forming bacterium *Clostridium botulinum*. BoNT serotypes are synthesized as an inactive single-chain polypeptide which is activated when cleaved into a 50 kDa light chain and a 100 kDa heavy chain. The heavy chain is responsible for transport of the light chain into the neuronal cytosol and the main pharmacological action is provided by the light chain which acts on the SNARE (soluble N-ethylmaleimide-sensitive factor attachment protein receptor) complex inhibiting the release of neurotransmitters into the synaptic cleft.

There are seven immunologically distinct serotypes from type A to type G which have been isolated. The most commonly used serotype within the lower urinary tract is BoNT-A. It is available in different commercial forms and the two most common preparations are onabotulinumtoxin A (onaBoNT-A) (Botox®; Allergan, Ltd., Irvine, USA) and abobotulinumtoxinA (aboBoNT-A) (Dysport; Ipsen Ltd., Slough, UK). Although these preparations have similarities, their manufacturing processes have different isolation, extraction, purification and stabilization processes (10). This results in products with different molecular characteristic and dosing requirements and they should not be considered as generic equivalents.

Detrusor overactivity (DO)

NDO and OAB remain the only approved indications for BoNT-A within the urinary tract. onaBoNT-A has received regulatory approval from the U.S. Food and Drug Administration (FDA) (11) and the UK Medicine and Healthcare Products Regulatory Agency (MHRA) (12). It is recommended by the majority of international bodies and guidelines as a second-line treatment for NDO or OAB in patients who have symptoms refractory to antimuscarinics or β3 adrenoceptor agonists (13,14).

Mechanism of action

BoNT-A appears to have a dual mechanism of action on both the motor and sensory pathways responsible for DO (15). The original research into BoNT-A was in skeletal muscle which suggested that the mechanism of action was solely due to inhibition of acetylcholine release from presynaptic efferent nerves (16). This occurs when BoNT-A enters the presynaptic neuron by binding to the synaptic vesicle 2 (SV2) receptor protein. BoNT-A enters the nerve by endocytosis and the light chain and heavy chain separate in the endosomal vesicle. The light chain is translocated into the cytosol where it cleaves the SNAP-25 protein which is an essential component for fusion of vesicles containing acetylcholine with the neuronal cell membrane (17,18). Blocking the release of acetylcholine inhibits parasympathetic signalling to the bladder, reducing involuntary detrusor contractions.

In addition to inhibiting detrusor activity, it was noted that patients described improvements in sensory symptoms which highlighted that BoNT-A may also modulate sensory functions in an unrelated mechanism to inhibition of acetylcholine release. Animal studies have shown that BoNT-A inhibits the release of a range of neurotransmitters from the urothelium including CGRP (10), substance P (11) and ATP (12). This is combined with decreasing expression of sensory receptors such as vanilloid (TRPV1) and purinergic (P2X3) receptors further modulate sensory function (13). Beyond the peripheral sensory effects, animal studies have found that BoNT-A may reach the CNS by retrograde axonal transport and have central antinociceptive activity (14). Both motor and sensory effects are reversible but regeneration of sensory receptors appears to take longer and it is the sensory effects which determine the duration of action of BoNT-A (19).

Techniques for injection and dosing

There remains no standardized injection technique and significant variability exists between centres. Factors which

vary include use of rigid or flexible cystoscopy, general or local anaesthetic, size of injection needle and optimal injection site. The technique was originally described in NDO patients using a collagen needle with a rigid cystoscope (5). However, many centres have adopted a minimally invasive, local anaesthetic approach known as the "Dasgupta technique" (20). The injections are performed using a flexible cystoscope and an ultra-fine 4 mm needle. Local anaesthetic is administered prior to the procedure with 2% intra-urethral lidocaine gel. The technique avoids risk of a general anaesthetic and has significant cost advantages (21). Procedure time is approximately 15–20 mins and it is well tolerated with low patient reported pain scores (22).

The majority of centres use an injection protocol which includes 20–30 injections sparing the trigone. Traditionally the trigone has been spared based on a theoretical risk of inducing vesicoureteral reflux (VUR). However, there remains discussion regarding the optimal injection sites and multiple studies have challenged the VUR theory using video urodynamics to show that trigonal injections do not induce VUR in both NDO (23) and OAB (24) patients. It has been suggested that protocols which include the trigone may have additional sensory benefits as the trigone has a high density of nociceptive bladder afferents (25). An randomized controlled trial (RCT) which compared trigone-sparing and trigone-including injection in found that the trigone injections improved overall symptom scores and urgency subscale scores in IDO patients (26). However, a recent meta-analysis by Davis *et al.* did not find any difference in short term efficacy between trigonal and extratrigonal injections (27).

Dosing

The licensed dose in NDO has been set at onaBoNT-A 200 U based on several phase 3 RCTs. These studies found no difference in efficacy outcomes between 200 and 300 U but the higher dose was associated with a significant risk of clean intermittent self-catheterization (CISC) (28,29). Similarly in OAB, the licensed dose is onaBoNT-A 100 U following several large dose ranging RCTs (30-32). These doses were seen as the optimal risk-benefit ratio but were lower than had been previously utilized in the early studies.

Clinical efficacy in NDO

The initial description of BoNT-A as a treatment for NDO was a pilot study by Schurch *et al.* who treated 21 patients with SCI using BoNT-A 200 or 300 U sparing the trigone (5). All patients had failed maximum anticholinergic treatment and were CISC dependent. At 6 weeks, 17 out of 19 patients were completely continent and ten patients had decreased anticholinergic requirements. There were also baseline improvements in urodynamic parameters including mean maximum cytometric capacity (MCC) and maximum detrusor pressure ($PDet_{max}$).

These promising initial results triggered several small placebo controlled, randomized studies evaluating the use of BoNT-A in NDO which are summarized in *Table 1* (33-35). The first RCT randomized 59 patients with SCI and MS to two doses of BoNT-A (200 and 300 U) and placebo saline injections (33). The primary end points were incontinence episodes which were reduced in the 200 U group at 24 weeks and in the 300 U group at 2 and 6 weeks. There was a significant improvement in quality of life (QoL) scores in both treatment groups compared to placebo. No difference was found in outcomes between the two doses which were expected as the study was not powered to detect differences between groups.

The highest level evidence is dominated by the results of two phase III, double-blind, placebo-controlled trials (28,29). These two pivotal phase III studies will be discussed together as their data has been pooled in subsequent post hoc analysis (36,37). It was following their publication that BoNT-A was approved for treatment of urinary incontinence secondary. The pooled data includes 691 patients with either MS (n=381) or SCI (n=310) who had >14 urgency incontinence (UI) episodes per week and had symptoms refractory to anticholinergics for >1 month duration. The cohort was randomized to onaBoNT-A 200 U, onaBoNT-A 300 U or placebo and the primary end point was change from baseline in mean UI episodes at week 6. Secondary outcomes included urodynamics parameters and incontinence quality of life (I-QoL) scores. At 6 weeks, there was a statistically significant improvement in UI episodes per week in both treatment arms compared to placebo regardless of NDO aetiology. In addition, a higher percentage of patients were dry at 6 weeks compared to placebo (MS: 41.5%; SCI: 30.9%). A dose comparison showed no additional treatment efficacy from a higher 300 U dose. In terms of secondary urodynamic end points there were significant improvements in MCC, number of involuntary detrusor contraction and $Pdet_{max}$ during first IDC. The detailed outcomes on UI episodes, urodynamic and QoL scores are shown in *Table 1*.

The long-term efficacy outcomes of BoNT-A injections have been evaluated in a 4-year, prospective, multicentre extension study (38). This study included 396 patients

Table 1 Summary of placebo controlled studies in NDO

Study	Patients (n)	Treatment arms & BoNT-A dose	UI episodes/week (baseline)	MCC, mL (baseline)	$Pdet_{max}$, cmH_2O (baseline)	QoL, mean (%), change *vs.* baseline	Duration of effect (weeks)	Duration of follow-up (weeks)
Schurch *et al.* 2005	59	Placebo: 21	−0.2 (3.0)	+45.0 (254.6)	−10.1 (79.1)	9	N/A	≥24
		onaBoNT 200 U: 19	−0.9 (1.84)†	+182.1 (260.2)†	−44.4 (77.0)†	61†	≥24	
		onaBoNT 300 U: 19	−1.5 (2.33)†	+169.1 (293.6)†	−62.2 (92.6)	56†	≥24	
Ehren *et al.* 2007	31	Placebo: 14	N/A	+10 (250.0)	−12 (58.0)	Significant improvement in Rx arm	N/A	26
		aboBoNT 500 U: 17		+180 (280.0)†	−52 (68.0)†		26	
Herschorn *et al.* 2007	57	Placebo: 28	−29 (270.0)	−29 (270.0)	+13 (72.0)	Significant improvement in Rx arm	N/A	36
		onaBoNT 300 U: 29	+224 (297.5)†	+224 (297.5)†	−27.5 (60.0)†		≥36	
Cruz *et al.* 2007	275	Placebo: 92	−13.2 (36.7)	+6.4 (41.5)	−10.1 (79.1)	+8.6	13	52
		onaBoNT 200 U: 92	−21.8 (32.5)†	−28.5 (51.7)†	−44.4 (77.0)†	+25.1†	42	
		onaBoNT 300 U: 91	−19.4 (31.2)†	−26.9 (42.1)†	−62.2 (92.6)	+25.9†	42	
Ginsberg *et al.* 2012	416	Placebo: 149	−8.8 (28.3)	−2.4 (50.9)	−10.1 (79.1)	+10	13	52
		onaBoNT 200 U: 135	−21.0 (32.3)†	−35.1 (51.3)†	−44.4 (77.0)†	+25†	37	
		onaBoNT 300 U: 132	−22.7 (31.1)†	−33.3 (47.1)†	−62.2 (92.6)	+35†	36	

NDO, neurogenic detrusor overactivity; †, P<0.05 *vs.* placebo; BoNT-A, botulinum toxin A; UI, urgency incontinence; MCC, maximum cytometric capacity; $Pdet_{max}$, maximum detrusor pressure; QoL, quality of life; N/A, not available.

from the original phase III studies who received up to six repeat injections. It showed that there were sustained improvements in UI episodes per week and I-QoL scores across treatment cycles. The median treatment duration was 9 months and no new safety concerns were identified.

An important issue to consider is that these phase III studies only included patients with multiple sclerosis (MS) and SCI. There is considerable heterogeneity in aetiology of NDO and we must rely on non-randomized studies to confirm that BoNT-A injections are effective in other NDO aetiologies such as Parkinson's, multiple system atrophy, chronic cerebrovascular accidents and spinal cord lesions (39,40). In terms of BoNT-A formulations, the majority of studies have investigated the use of onaBoNT-A, but there is evidence for the clinical efficacy on aboBoNT-A. A placebo controlled RCT by Ehren *et al.* found a reduction in UI episodes, urodynamic parameters and QoL scores using aboBonT-A 500 U injections (34).

Clinical efficacy in OAB

The use of BoNT-A injections as a treatment for OAB or IDO has grown rapidly since first described in 2001 (6,7). During this time, the definition of OAB has moved to a symptom-based clinical diagnosis characterized by urinary urgency usually accompanied by frequency and nocturia with or without UI in the absence of urinary tract infection (UTI) (41). Sahai *et al.* reported the first randomized , double-blind, placebo-controlled trial which evaluated the efficacy and safety of onoBoNT-A 200 U in patients with IDO (42). The primary end point was change in MCC which was found to have significantly increased at 3 months. There were also improvements in QoL scores, OAB symptoms and urodynamic parameters in favour of onaBoNT-A compared to placebo. The detailed results are summarized in *Table 2*. Following this study, two other small RCT were published showing similar results in female patients (43) and across different doses of onaBoNT-A (200 and 300 U) (44). A meta-analysis of these early RCTs by Anger *et al.* (45) confirmed the efficacy of BoNT-A at improving OAB symptoms and QoL scores.

Subsequently, there have been several dose-escalation placebo-controlled studies to establish the optimal BoNT-A dose (30-32). The largest was a phase II, multi-centre, double-blind RCT by Dmochowski *et al.* which randomized 313 patients to different doses of onaBoN-T (50, 100, 150, 200 and 300 U) and placebo. The study included both patients with IDO and bladder oversensitivity, defined as OAB symptoms without demonstrable DO. The authors concluded that there was a significant improvement in OAB symptoms and QoL scores at all doses of 100 U and above. The presence of DO was not a predictive factor for outcome. A non-parametric analysis found that the reduction in urgency urinary incontinence (UUI) was dose dependent. The lower dose of 50 U was not as effective as higher doses. There was minimal additional benefit at doses above 150 U and these were associated with significantly higher rates of raised for post-void residual (PVR) and need for CISC. Similar findings were identified by a subsequent smaller dose ranging study by Denys *et al.* which compared 50, 100, 150 U onaBoNT-A with placebo and found that the two highest doses were most efficacious but 100 U had a lower risk of raised PVR and need for CISC (32). Based on these dose-ranging studies, the dose was set at 100 U onaBoNT-A as the optimal balance between treatment efficacy and AEs.

The final step to licensing was the completion of two large, placebo-controlled phase III studies (46,47) which have been pooled by Sievert *et al.* giving a sample size of 1,105 patients (48). The enrolled patients had and ≥3 UI episodes per three days, ≥8 micturitions per day and were randomized to 100 U onaBoNT-A (n=557) and placebo (n=548). The study found a significant decline in urinary urgency incontinence (UUI) episodes per day in the treatment arm compared to placebo (–2.80 *vs.* –0.95 episodes/day; P<0.001). At week 12, full continence was achieved in 27.1% of onaBoNT-A group *vs.* 8.4% in the placebo group (P<0.001). The median time to request re-treatment was 24 weeks for onaBoNT-A compared to 12 weeks in placebo group.

Previous studies had suggested that BoNT-A was more likely to be effective in patients who were unable to tolerate anticholinergics rather than poor medication efficacy (49). However, a sub-analysis in the phase III studies showed that efficacy of BoNT-A was not affected by the reason for discontinuation of medical therapy or the number of prior anticholinergics.

The long-term efficacy of onaBoNT-A has been recently evaluated in a prospective, multicenter, 3.5-year extension study. This included 839 patients who had been enrolled in the original phase III studies and were invited to continue long-term follow-up (50). The cohort received up to six repeat injections and there was a consistent absolute reduction of UI episodes, ranging from –3.1 to –3.8, across each treatment cycle. The median duration of effect was 7.6 months and no new AEs were identified.

Table 2 Summary of placebo controlled studies in OAB

Study	Patients (n)	Treatment arms & BoNT-A dose	UI episodes (baseline)	Micturition (baseline)	MCC, mL (baseline)	Dry, %	QoL (baseline)	Duration of effect
Sahai *et al.* 2008	36	Placebo: 18	–0.7/day (3.91)†	–1 (14.3)	–29.5 (198.1)	12.0	IIQ-7 & UDI-6 significant improvement in BoNT-A arm	≥24 weeks
		onaBoNT 200 U: 18	–3.1 (4.98)/day†	–7.51 (15.4)	+131.4 (181.8)	50.0		
Brubaker *et al.* 2008	43	Placebo: 15	–1 (19.0)/day	N/A	N/A	N/A	PGI-I significant improvement in BoNT-A arm	26 weeks
		onaBoNT 200 U: 28	–18 (21.0)/day					
Flynn *et al.* 2009	22	Placebo: 7	+0.7 (8.0)/day	–0.8 (11.1)	No statistical difference	N/A	IIQ-7 & UDI-6 significant improvement in BoNT-A arm	N/A
		onaBoNT 200 U: 15	–4.5 (7.9)/day	–1.3 (10.5)				
Dmochowski *et al.* 2010 & Roverner *et al.* 2011	313	Placebo: 44	–17.4 (32.5)/week	–8.3 (73.3)/week	+49.5 (267.1)	15.9	+17.9 (35.9)	N/A
		onaBoNT 50 U: 57	–20.7 (30.3)/week	–15.3 (76.3)/week	+50 (262.9)	29.8	+29.8 (32.3)	18 weeks
		onaBoNT 100 U: 54	–18.4 (27.8)/week	–21.7 (80.3)/week	+71 (255.0)	37.0	+32.9 (34.3)	24 weeks
		onaBoNT 150 U: 59	–23.0 (28.3)/week	–18.8 (76.5)/week	+101.7 (258.4)†	40.8	+35.2 (30.5)	>36 weeks
		onaBoNT 200 U: 53	–19.6 (24.1)/week	–19.7 (76.7)/week	+91.5 (280.1)	50.9	+37.1 (32.0)	>36 weeks
		onaBoNT 300 U: 56	–19.4 (26.8)/week	–21.2 (75.6)/week	+130.8 (271.7)†	57.1	+39.7 (34.5)	>36 weeks
Deny *et al.* 2012	107	Placebo: 31	Improvement 30%>50%	–0.9 (11.2)/day	24 (229.3)	10.7	I-QOL improvement in majority of patients on 100 & 150 U	5–6 months
		onaBoNT 50 U: 23	37%>50%	–1.6 (12.7)/day	17 (212.2)	15.8†		
		onaBoNT 100 U: 23	68% with >50%	–3.8 (12.6)/day†	20 (249.3)	55.0†		
		onaBoNT 150 U: 30	58% with >50%	–4.2 (12.8)/day†	21 (220.5)	50.0†		
Nitti *et al.* 2013	557	Placebo: 277	–0.87 (5.1)/day	–0.91 (11.2)/day	N/A	6.5	IIQ-7 & KHQ significant improvement in BoNT-A arm	N/A
		onaBoNT 00 U: 280	–2.65 (5.5)/day†	–2.15 (12.0)/day†		22.9†		>24 weeks
Chapple *et al.* 2013	548	Placebo: 271	–1.03 (5.7)/day	–0.8 (11.8)/day	N/A	N/A	IIQ-7 & KHQ significant improvement in BoNT-A arm	N/A
		onaBoNT 100 U: 277	–2.95 (5.5)/day†	–2.6 (12.0)/days†				>24 weeks

OAB, overactive bladder; BoNT-A, botulinum toxin A; UI, urgency incontinence; MCC, maximum cytometric capacity; QoL, quality of life; $Pdet_{max}$, maximum detrusor pressure; †, P<0.05 *vs.* placebo; N/A, not available.

AEs

The most common AEs from BoNT-A injections are UTI and voiding dysfunction requiring CISC. The pooled analysis of phase 3 trials reported uncomplicated UTI rates of 53.8% in NDO (37) and 25.5% in OAB (48). The definition of UTI is variable between studies with the OAB trials required a positive urine culture while NDO trials based the diagnosis on clinical assessment. Urinary retention and need for CISC is the next most common AE and these are known to be dose dependent. In NDO, for patients who were not CISC dependent at baseline, the risk of requiring *de novo* CISC was 30.8% and 44.0% in onaBoNT-A 200 and 300 U groups respectively (37). In OAB, the risk of retention was 5.8% for onaBoNT-A compared to 0.4% with placebo (48). The risks of systemic side effects including generalised muscle weakness, dysphagia and respiratory depression are very rare.

The long-term extension studies did not identify any new AEs following repeat injections. There had been early concerns that repeat injections could cause fibrosis, reduced bladder compliance and worsen of overactive symptoms but this has not been demonstrated in clinical studies (51).

Bladder pain syndrome (BPS)

Interstitial cystitis (IC) or BPS is a chronic condition characterized by debilitating bladder pain of unknown aetiology. The recent EAU guidelines have recommended a new nomenclature in which BPS is the singular term used and combinations such as PBS/IC are no longer recommended (52). The guidelines defines BPS as a recurrent pain, perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than 6 months duration and not associated with obvious local pathology (52). There is no standardized treatment regimen but there are a multitude of therapies which are often unsuccessful at completely eradicating the syndrome. The current treatments are usually performed in a stepwise approach including physiotherapy, oral medications, endourological procedures (intravesical installations, hydrodistention, laser fulguration) neuromodulation and cystectomy. Although BoNT-A injections remain unlicensed for BPS, the recent AUA guidelines have recommended them as a fourth line treatment in patients who failed conventional options (53).

Mechanism of action

The aetiology and pathogenesis of BPS are still not clearly understood and this contributes to the challenge of identifying effective treatments (54). Various aetiological factors have been suggested such as subclinical or chronic infection, autoimmune mechanisms, allergic processes and exposure to toxins (55). The predominate histological findings in BPS are denudation of the glycosaminoglycan urothelial surface layer, mucosal ulceration, neuronal upregulation and inflammatory cell activation, which suggests an underlying inflammatory process in the disease (56). BoNT-A has been hypothesized as having a multifactorial action by improving urothelial dysfunction, reducing inflammatory cell activation and modulating sensory function (57). In addition to the sensory effects, animal studies have shown that BoTN-A inhibits sensory neuropeptide release in inflammatory rats suggesting a potential clinical benefit in reducing neurogenic inflammation (58)

Techniques for injection and dosing

The general injection technique is similar to DO and the majority of studies use a dose of 100 or 200 U onaBoNT. A RCT comparing these doses found that rates of AEs were higher in the 200 U group with no significant difference in efficacy (59). There is no consensus on the optimum injections site in BPS (60). The discussion regarding injections in the trigone has been of increased importance in BPS given the high density of nociceptive bladder afferents in the trigone (25). The majority of BPS studies have shown that BoNT-A injections can produce significant improvements in pain, symptom scores and urodynamic parameters (8,25,61,62). However, trigone sparing injection protocols have not produced consistent clinical improvements (59) which suggests that trigone-including protocols may be important. However, there is a need for a specific comparison study to formally evaluate this.

Clinical efficacy

There have been three published placebo-controlled RCTs providing level 1 evidence for BoNT-A injections in BPS (59,63,64). These studies have significant heterogeneity in terms of inclusion criteria, definition of BPS, efficacy outcomes, BoTN-A dose and site of injection. The results are summarized in *Table 2*. The first RCT did not show any improvement in pain scores (63) although this was not unexpected as the study used a novel periurethral injection technique with the aim of inhibiting urethral, visceral and

somatic afferent fibres. A subsequent RCT using a standard suburothelial injection technique compared the efficacy of hydrodistention alone with two doses of onaBoNT-A injections (100 and 200 U) followed by hydrodistention. In this study pain scores, functional bladder capacity and cystometric bladder capacity were significantly improved in the onaBoNT-A groups compared to the control group at 3 months follow-up (P=0.02).

These results were confirmed in a recent multi-centre, randomized, double-blind, placebo-controlled trial which recruited 60 patients randomized to BoTN-A 100 U or normal saline injections. All received twenty suburothelial injections sparing the trigone after hydrodistention under general anaesthetic. The primary outcome measure was reduction in VAS pain score which was found to be significantly improved in the BoNT-A group compared to the control (–2.62 *vs.* –0.9, P=0.021) (64). There was no significant difference demonstrated in urodynamic parameters apart from maximum bladder capacity which was higher in the BoNT-A group.

Given that BPS encompasses a heterogeneous spectrum of disorders, it is hypothesized that it may be more effective in certain sub-groups. Lee *et al.* compared the efficacy of BoNT-A in the presence or absence of Hunner's ulcers (65) and found no benefit in ulcerative IC across VAS scores, O'Leary-Sant scores, frequency and bladder capacity. The study concluded that BoNT-A may only be effective in non-ulcerative IC with approximately 50% of patients reporting a clinical benefit from treatment.

AEs

The AEs are similar to those reported in NDO and OAB studies. The risk has also been shown to be dose related in an RCT by Kuo *et al.* which found a higher incidence of dysuria and urinary retention with onaBonT-A 200 U compared to onaBoNT-A 100 U (59).

Detrusor sphincter dyssnergia (DSD)

The use of BoNT-A injections has been applied to target organs outside the bladder including the external urethral sphincter. DSD is characterized by involuntary sporadic contractions of the urethral sphincter during a detrusor contraction, due to a CNS lesion between the sacral spinal cord and pontine micturition centre (66). It can lead to incomplete bladder emptying, high pressure retention, VUR and renal impairment. DSD is typically seen in patients with supra-sacral spinal lesions (SCI), MS, myelomeningocele and acute transverse myelitis (67). The first application of BoNT-A within the lower urinary tract was by Dykstra *et al.* who injected BoNT into the external urethral sphincter of patients with SCI to treat (4). The effects can be treated by CISC but this may not be physically possible for certain patient groups such as MS and quadriplegic patients. Therefore, BoNT-A injections for DSD have been primarily used in patients who were unable to perform CISC as an alternative to surgical sphincterotomy.

Mechanism of action

The effects of BoNT-A on striated muscle has been extensively studied in conditions associated with dystonic and spastic muscular hyperactivity (68). By blocking the presynamic release of acetylcholine, there is chemo-denervation of the target muscle. The aim is to produce a "chemical sphincterotomy" where there is sufficient reduction in external sphincter tone to improve voiding dysfunction. The electromyography after BoNT-A injections in Dykstra's *et al.*'s original report confirms a decrease in maximum urethral pressure (MUP) by an average of 27 cmH_2O (4).

Techniques for injection and dosing

A range of injection techniques into the external urethral sphincter have been described including a transurethral, paraurethral and transperineal approach with or without electromyography guidance (69). The efficacy appears to be equivalent across each technique and the particular approach will be determined by operator experience and equipment availability (70). The transurethral approach has been frequently described in men and involves BoNT-A injected directly into the external urethral sphincter under rigid or flexible cystoscopic guidance (67). The injections are placed into the sphincter at four to eight sites, typically in 3, 6, 9 and 12 o'clock positions, and the needle needs to be inserted at a depth of approximately 1 cm, which is deeper than in urethral bulking agents, to avoid the suburothelial space and ensure the drug reaches the sphincter (71). This approach may require a general or spinal anaesthetic but has been described under local anaesthetic. A periurethral approach can be performed in women which involves inserting a needle transcutaneously, adjacent to the urethra, at a depth of approximately 1.5 cm

to reach the external sphincter (72).

Transperineal techniques have been well described combined with electromyography (EMG) (73) or transrectal ultrasound (70) for localisation of the external urethral sphincter. EMG-guided methods are technically challenging and it is difficult to exclude interference from the surrounding perineal muscles (74). Nevertheless, MRI studies have shown that an experienced operator using EMG can accurately target the external urethral sphincter (74). An alternative is transrectal ultrasound-guided transperineal injection which more clinicians are gaining experience of as an investigation in prostatic disease. A transrectal three-dimensional multiplanar transducer probe can be used to identify the hypoechoic external urethral sphincter located just distal to the prostatic apex (70).

The dose of BoNT-A injected into the external urethral sphincter ranges from 50 to 200 U of onaBoNT-A (75,76) or 150 U of aboBoTN-A (77). The drug is usually reconstituted in 2 to 4 mL of normal saline.

Clinical efficacy

Since Dykstra's initial report, there have been only three small RCTs completed in DSD which are summarized in *Table 2*. A small RCT was conducted by Dykstra *et al.* 1990 including five patients with SCI randomized to BoNT-A 140 U and normal saline (78). At day 21, there was a decrease in MUP, PVR and maximum bladder pressure in the treatment arm. The results from the placebo group are not reported so no comparisons can be drawn regarding any placebo effect. Another small active-comparator RCT randomized 13 patients to BoNT-A 100 U and lidocaine 0.5%. This trial did find a significant decrease in PVR in the treatment group compared to lidocaine (–159.4 *vs.* 49.8 mL) although the mean PVR remained elevated at above 100 mL (79). A larger multi-centre RCT by Gallien *et al.* randomized 86 patients with MS to a single transperineal injection of BoNT-A 100 U or saline as placebo (80). The primary outcome measure was PVR, measured using catheterisation, and secondary outcomes included voiding and urodynamic variables. There was no significant difference in PVR between the two groups (P=0.45) although some differences were found in urodynamic parameters.

The results from the RCT conflict with subsequent small heterogeneous observational studies which demonstrate that PVR is significantly reduced following BoNT-A injections. Other observational studies have found improvements in QMax, maximum urethral closure pressure, frequency of voiding and QoL. A meta-analysis of SCI patients also found that there was a mean PVR decrease from 251.8 to 153.0 mL for up to 6 months (81).

Nevertheless, a recent Cochrane review which reviewed all of this literature concluded that the current evidence for BoNT-A in DSD is of limited quality due to the small number of participants in level 1 trials and the risk of bias from observational studies (67). The review noted that a surgical sphincterotomy may be the superior treatment as it provides greater efficacy and longer duration effect.

AEs

BoNT-A injections were generally well tolerated with minimal adverse side effects. Dykstra *et al.* 1990 injected 140 U BoNT-A followed by 240 U at subsequent sessions and reported three episodes of transient muscle weakness. This was thought to be due to a short inter-injection interval of 1 week (78) and the authors have addressed this by waiting a minimum of 2 weeks between injections (67). Observational studies have reported the exacerbation of stress urinary incontinence following injection due to the denervation of the external urethral sphincter. This has been shown to be a major cause of patient dissatisfaction following the treatment (82). Therefore it is important to appropriately counsel them about the risk of stress incontinence before commencing this off-licence treatment.

BPH

Since first reported in 2003, there has been significant interest in BoNT-A prostatic injections as an alternative treatment for BPH (9). Current medical treatment for BPH is associated with autonomic and sexual side effects and a proportion of patients' progress despite combination therapy. Surgical techniques are associated with long-term morbidity including retrograde ejaculation and erectile dysfunction and a less invasive alternative is highly desirable.

Mechanism of action

The exact mechanisms of action remains under discussion but a dual mechanism has been proposed in which BoNT-A injections act on both the static and dynamic components of BPH (83). The prostate receives autonomic innervation from cholinergic fibres supplying predominately the epithelium and noradrenergic fibres supplying the

prostatic stroma (84). Muscarinic receptors are expressed in abundance on the prostatic epithelium (85,86) and it is postulated that these play a key role in prostatic growth in combination with testosterone (87). BoNT-A injections inhibits the influence of acetylcholine on these receptors resulting in disruption of the excessive growth (static) component of BPH. Atrophy of the gland and subsequent reduction in prostate volume should improve the obstructive symptoms associated with BPH.

The regulation of the smooth muscle (dynamic) component was originally thought to be due to an inhibition of the effects of noradrenaline on the prostatic stroma (84). More recent studies have suggested that BoNT-A effects on stromal smooth muscle is due to a combination of down regulating α1A-adrenoceptors, vacuoles forming in stromal smooth muscle cells and inhibition of norepinephrine release from sympathetic fibres (83).

Techniques for injection and dosing

There is no standardized injection technique but the majority of studies describe a similar technique of two injections of equal volume (2 mL) into the transition zone of each lateral prostatic lobe (9,88-93). Kuo *et al.* (94) described an alternative technique of ten injection sites including the middle lobe while Marberger *el al*. (95) describes a three site technique which includes the cranial, middle and caudal parts of each lateral lobe.

Most studies describe BoNT-A injections using a transperineal approach (9,88-92,94,96) (*Table 3*). It might be expected that the transrectal route would be associated with a high risk of infection due to bacterial contamination from rectal flora. This has been demonstrated in prostatic biopsy where the transperineal approach has an infection rate approaching zero (97) compared to up to 6.3% after transrectal biopsy (98). The transrectal and transperineal approach were compared in a large randomized control trial by Marberger *et al.* although this was not part of the trial protocol and the comparison was only possible due to an amendment to the trial protocol. There was no significant difference in clinical efficacy based on route of administration. However, a high rate of prostatitis was reported in the transrectal group compared to the transperineal group.

The most common dosing is with onaBoNT-A 200 U distributed equally into each lateral lobe. However, the two phase II, dose escalation, RCTs concluded that there was no significant difference in efficacy or AEs between 100–300 U (95,99). Crawford *et al.* concludes that 100 U dose may be preferable based on the similar efficacy and adverse effects with reduced cost. An alternative approach is to stratify the dose based on prostate size. Chuang *et al.* used 100 U for prostate volumes <30 mL and 200 U for prostate volumes >30 mL (96).

Clinical evidence

The potential application of BoNT-A for BPH in humans was first investigated by Maria *et al.* in 2003 (9). This placebo-controlled RCT randomized 30 patients with symptomatic BPH to placebo or BoNT-A 200 U. The primary outcome measures were improvement in QMax and subjective BPH symptomatic improvement based on the AUA symptom improvement score. At 2 months follow-up, there had been a subjective symptom improvement in 87% of the treatment group and 10% of the control group (P=0.0007). These early results were supported by several small open label case series published between 2003 and 2009. These studies lacked placebo control but they seemed to confirm the beneficial effects of BoNT across a variety of inclusion criteria and outcome measures including International Prostate Symptom Score (IPSS), QMax, PVR, QoL scores and urodynamic parameters (88-91,94,96,100). The results of these studies are summarized in *Table 4*.

Based on these results, several large RCTs have been undertaken with conflicting results. Two double-blind, randomized , placebo controlled trials which included approximately 700 patients concluded that there was no significant difference in improvement in IPSS score between placebo and various does of BoNT-A (92,95). A systematic review and meta-analysis which combined all three RCTs (REF) confirmed that the current level 1 evidence does not support any difference in efficacy between BoNT-A injections and placebo (101).

The primary issue from the placebo controlled RCTs is that men with LUTS/BPH appear to have a large placebo response to injection therapy into the prostate. The RCTs have reported a large placebo effect from the sham injection treatment with improvements in IPSS score of up to 25%. This issue is being addressed by the PROTOX study which is a non-inferiority RCT comparing optimal medical treatment with BoNT-A injections. At present, the initial results have been presented in international conferences and are yet to undergo peer review (93) (*Table 3*).

However, the early result suggests that after 4 months follow-up BoNT-A injections are not inferior to optimised medical treatment based on IPSS score. Moreover, the post

Table 3 Summary of studies on BoNT-A for BPH

Study	Design	Level of evidence*	Patients (n)	Treatment arms & BoNT-A dose	Injection technique	Outcome measures (1. primary outcome; 2 secondary outcome)	Follow-up (months)	Efficacy outcomes	Adverse events
Maria *et al.* 2003	Randomized, placebo controlled	1b	30	Placebo: 15; BoNT-A 200 U: 15	Transperineal: 4 injection sites; 2 per lateral lobe	1. AUASI & Qmax; 2. prostate volume, PSA & PVR	19.6[#]	Improvements in: AUASI by 62%; Qmax by 90%	No adverse events
Chuang *et al.* 2005	Prospective case series	3	16	BoNT-A 200 U: 16	Transperineal: 4 injection sites; 2 per lateral lobe	IPSS, QoL index, Qmax, PVR and prostate volume	10.0[†]	Improvements across all parameters (IPSS 52.6%, QOL 44.7%, Qmax 39.8%, prostate volume 13.3%)	No adverse events
Kuo *et al.* 2005	Prospective case series	3	10	BoNT-A 200 U: 10	Transperineal: 10 injections sites; across all lobes	Prostate volume and urodynamic parameters	12.0[†]	Decrease in voiding pressure, PVR & prostate volume	No adverse events
Chuang *et al.* 2006	Prospective case series	3	41	BoNT-A 100 U: 21; BoNT-A 200 U: 20	Transperineal: 2–4 injection sites; 1–2 per lateral lobe	IPSS, QoL index, Qmax, PVR and prostate volume	12.0[†]	Improvements in all parameters at both doses	No adverse events
Chuang *et al.* 2006	Prospective case series	3	8	BoNT-A 200 U: 8	Transperineal: 4 injection sites; 2 per lateral lobe	IPSS, QoL index, Qmax, PVR and prostate volume	4.75[†]	Improvements across all parameters (IPSS 73.1%, QOL 61.5%, Qmax 72.0%, prostate volume 18.8%)	Not reported
Reddy *et al.* 2008	Prospective case series	3	21	BoNT-A 200 U: 21	Transrectal: injection technique not specified	Prostate volume, Qmax, PVR & PSA	3.0[†]	Improvements across all parameters	No adverse events
Brisinda *et al.* 2009	Prospective case series	3	77	BoNT-A 200 U: 77	Transperineal: 4 injection sites; 2 per lateral lobe	AUA symptom score, PSA, prostate volume, Qmax, PVR	Up to 30	Improvements across all parameters	No adverse events
Silva *el al.* 2009	Prospective case series	3	16	BoNT-A 200 U: 16	Transperineal: 4 injection sites; 2 per lateral lobe	IPSS, QoL index, Qmax, PVR and prostate volume	10.0[†]	Improvements across all parameters	No adverse events
Crawford *et al.* 2011	Dose-ranging, randomized, controlled	1b	134	BoNT-A 100 U: 68; BoNT-A 300 U: 66	Transrectal: 4 injection sites; 2 per lateral lobe	1. AUASI, Qmax & AEs; 2. prostate volume, & PVR	12.0[†]	100 U arm improvements: AUASI-6.9, QMax-2.2 mL/s; 300 U arm improvements: AUASI-7.2, QMax-2.3 mL/s	Similar AE rate across both arms: 100 U: 2.5%; 300 U: 2.7%
Marberger *et al.* 2013	Dose-ranging, randomized, placebo controlled	1b	380	Placebo: 94; BoNT-A 100 U: 95; BoNT-A 200 U: 94; BoNT-A 300 U: 97	Transperineal [63] or transrectal [311]: 6 injection sites; 3 per lateral lobe	1. IPSS score at 12 weeks; 2. QMax, TPV, TZV	18.0[†]	Improvements in IPSS not significantly different b/t BoNT-A & placebo	Similar AE rate across all arms
McVary *et al.* 2014	Randomized, placebo controlled	1b	315	Placebo: 157; BoNT-A 200 U: 158	Transrectal: 4 injection sites; 2 per lateral lobe	1. IPSS score at 12 weeks; 2. QMax, prostate volume & PVR	6.0[†]	Improvements in IPSS not significantly different b/t BoNT-A & placebo	Similar AE rate across both arms
Delongchamps *et al.* 2016 [conference paper]	Randomized, active comparator controlled	1b	127	Medical therapy: 63; BoNT-A 200 U: 64	Transrectal: 4 injection sites; 2 per lateral lobe	1. IPSS score at 120 days; 2. QMax, prostate volume & PVR	18.0[†]	BoNT-A not inferior to medical treatment based on IPSS score	Serious AEs in BoNT-A arm: haematuria: 3; prostatitis: 2; AUR: 2

BoNT-A, botulinum toxin A; BPH, benign prostatic hyperplasia; *, level of evidence was rated according to a modified Oxford system as used by the European Urology Association (Thuroff *et al.*, 2011); [†], mean; [#], median ; IPSS, International Prostate Symptom Score; QoL, quality of life; PVR, post-void residual.

Table 4 Summary of RCTs for BPS and DSD

Study	Design	Patients (n)	Treatment arms & BoNT-A dose	Injection technique	Outcome measures (1. primary outcome; 2. secondary outcome)	Follow-up	Efficacy outcomes	Adverse events attributed to BoNT-A
BPS								
Gottsch *et al.* 2010	Double-blind, placebo-controlled RCT	20	Placebo: 11; BoNT-A 50 U: 9	Periurethral injections	1. CPSI-F symptom score; 2. adverse events	3 months	No improvement in CPSI score at 3 months	No adverse events
Kuo *et al.* 2009	Active comparator controlled RCT	70	HD alone: 23; BoTN-A 100 U: 29; BoNT-A 200 U: 15	Posterior and lateral bladder walls	1. GRA, VAS, ICSI & ICPI symptom scores; 2. voiding diary & urodynamics parameters	Up to 24 months	1. VAS reduction significant only in BoNT-A group; 2. no difference in 100 *vs.* 200 U in response	Haematuria 2; dysuria: 10; urinary retention: 3; UTI: 3
Kuo *et al.* 2016	Double-blind, placebo-controlled RCT	60	HD followed by: placebo: 20; BoNT-A 100 U: 40	Trigone sparing injections	1. VAS score at 8 weeks; 2. voiding diary & urodynamic parameters	2, 4 & 8 weeks	1. Significant reduction in VAS score (P=0.02); 2. no difference in other outcomes apart MBC	Haematuria: 1; dysuria: 16; UTI: 2
DSD								
Dykstra *et al.* 2000	Double blind, placebo controlled RCT	5	Placebo: 2; BoNT-A: 140 U: 3	Electromyography transperineal injection	MUP, PVR, $Pdet_{max}$	2 months	MUP by 25 cm/H_2O; PVR ↓ by 12 5 mL; pDet ↓ by 20 mL/H_2O	Generalised weakness: 3; autonomic dysreflexia: 2
De Seze *et al.* 2002	Double blind, active comparator controlled RCT	13	Lidocaine 0.5%: 8; BoNT-A 100 U: 5	Electromyography transperineal injection	Voiding diary, PVR, satisfaction score & MUP	To be done: <3 months: 31%; >3 months: 46%	Significant decrease in PVR (P<0.01) & MUP (P 0.04)	Transient urinary incontinence: 1
Gallien *et al.* 2005	Double blind, placebo controlled RCT	86	Placebo: 41; BoNT-A 100 U: 45	Electromyography transperineal injection	1. PVR after 30 days; 2. urodynamic variables &VAS	4 months	1. No difference in PVR Δ; 2. significant improvement in voiding volume & $Pdet_{max}$	UTI: 16; MS attacks: 6; urinary incontinence: 2; faecal incontinence: 1

RCTs, randomized controlled trials; BPS, bladder pain syndrome; DSD, Detrusor sphincter dyssynergia; BoNT-A, botulinum toxin A; HD, hydrodistention; UTI, urinary tract infection; MUP, maximum urethral pressure; PVR, post-void residual; $Pdet_{max}$, maximum detrusor pressure.

hoc analysis of one of the recent RCTs (95) has identified a subgroup of prior α blocker users who did have a significant reduction in IPSS score with BoNT-A 200 U compared to placebo (95). Therefore, BoNT-A prostatic injection may have a role as an alternative to medical treatment or there may be a subset of patients on maximum medical therapy who may benefit from BoNT-A as an adjunct.

Nevertheless, there remains conflicting level 1 evidence and therefore BoNT-A prostatic injection cannot be recommended for routine use in clinical practice until further research is completed. This is supported by a number of international BPH guidelines which have been updated without including BoNT-A injections (102).

AEs

The early studies did not report any significant AEs. The larger high quality randomized control studies reported an AE rate of 30% (92). These were classified as mild or moderate in severity and the most common AEs are haematuria (12.7%) and haematospermia (8.2%). Prostatitis appears to be the most common infection related complication and in one study was higher in the group undergoing BoNT-A injections via the transrectal route (95). Given that there was no significant different in any AE between placebo and treatment arms, it is likely that these are related to the injection procedure rather than BoNT-A treatment.

Future developments

There is ongoing research into alternative mechanisms to deliver BoNT-A in order to improve tolerability of the treatment and reduce AEs. The high molecular weight of BoNT-A (150 kDa) has restricted administration to cystoscopic injection in order to reach the suburothelium, but injections are associated with discomfort, risk of UTI and urinary retention. There have been promising development with liposome enucleated BoNT-A instillations which may provide a mechanism of transporting BoNT-A across the urothelium (103). The early pilot studies in clinical practice have shown encouraging results (104-106). Chuang *et al.* published on the use of intravesical liposome complex in BPS patients and found a significant decrease in urinary frequency and nocturia compared to baseline (104). Kuo *et al.* has published a RCT study in OAB patients treated with 80 mg liposomes and 200 U BoNT-A or normal saline, showing similar improvement in frequency and urgency episodes but no significant change in UUI episodes (105). The treatment did not cause any UTIs, raised PVRs or episodes of retention and may be a promising alternative approach to cystoscopic injection.

Conclusions

Over the last decade, BoNT-A has developed into valuable a treatment option for a range of lower urinary tract conditions. Regulatory phase III trials have conclusively demonstrated that for both NDO and OAB, BoNT-A decreases UII, improves urodynamic parameters and increases QoL. There is robust data for long-term efficacy and safety outcomes across multiple treatment cycles.

Other applications remain off-license but there is accumulating level 1 evidence that BoNT-A is beneficial in the treatment of BPS. Its use is likely to grow following recommendation in the AUA guidelines as a fourth line treatment options. In contrast, there is a lack of high quality evidence with DSD and no definite recommendation can be made based on the current evidence. Finally, the results for the treatment of BPH have been variable and recent high quality RCTs have suggested no benefit over placebo so at present it cannot be recommended for routine clinical practice.

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Footnote

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