# Chapter 15
# Botulinum Toxin Treatment in Urological Disorders


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**Abstract** Botulinum toxin (BoNT) injection has been widely accepted by the urology and urogynecology medical communities as a safe and effective treatment for refractory urinary incontinence based on two decades of published literature. Currently, there are two approved genitourinary indications for botulinum toxin within the United States. OnabotulinumtoxinA (onaBoNTA) 200 units for the treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition (e.g., spinal cord injury, multiple sclerosis) in adults who have an inadequate response to or are intolerant to an anticholinergic medication was approved by the FDA in 2011. In addition, onaBoNTA 100 units for the treatment of overactive bladder with symptoms of urinary incontinence, urgency, and frequency, in adult patients who have an inadequate response to or are intolerant to an anticholinergic medication was approved by the FDA in 2013. We will update the reader on the latest application of botulinum toxin for urologic indications with a focus on bladder injections as well as on potential uses of BoNT in the prostate and pelvic floor.

**Keywords** Neurogenic detrusor overactivity · Overactive bladder · Benign prostatic hyperplasia · Interstitial cystitis · OnabotulinumtoxinA · AbobotulinumtoxinA

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## Introduction

The first application of botulinum toxin (BoNT) within the genitourinary system was not into the bladder but rather the external urethral sphincter. In 1988, Dyskstra and colleagues injected BoNT into the skeletal muscle urethral sphincter of spinal cord-injured (SCI) patients to treat detrusor sphincter dyssynergia [14]. Just over a decade later, Schurch and colleagues revolutionized the care of SCI patients through their novel application of BoNT into bladder smooth muscle to treat neurogenic detrusor overactivity in 21 SCI patients that failed high-dose anticholinergic medications [29, 30]. Their clinical success was confirmed by basic science experiments by Smith and colleagues that demonstrated that BoNT impaired electrically evoked neurotransmitter release from bladder tissue that resulted in diminished bladder contractile activity [31, 32]. These early results of exciting and promising initial off-label use of BoNT led to a registry trial and two Phase III multicenter, double-blind, placebo-controlled trials that led to the 2011 regulatory approval of onabotulinumtoxinA (onaBoNTA), at 100 and 200 units, for the treatment of urge incontinence due to NDO [11, 17]. Subsequently, phase III multicenter trials led to the 2013 regulatory approval of onaBoNTA for the treatment of idiopathic overactive bladder (OAB) without neurological diseases and refractory to anticholinergics [9, 27].

Other applications for BoNT include benign prostatic hyperplasia (BPH) and interstitial cystitis/bladder pain syndrome (IC/BPS). McVary et al. [26] reported on a phase 2 randomized clinical trial comparing onaBoNTA 200 U to placebo for the treatment of BPH, but no differences were seen in the primary and majority of secondary outcome parameters. For the treatment of IC/BPS, Kuo and Chancellor [24] reported a signal of efficacy in the off-label use of BoNT in the bladder pain score in IC/BPS patients. BoNT is currently listed as a fourth-line treatment in the American Urological Association guideline for the treatment of IC/BPS [19].

## Neurogenic Detrusor Overactivity

### *Clinical Trials*

Neurogenic detrusor overactivity (NDO), most common in MS and SCI, but also seen in other neurological diseases including stroke and Parkinson's disease, is characterized by the presence of involuntary detrusor contractions (IDC) during filling cystometry [7]. NDO, particularly in the presence of detrusor sphincter dyssynergia, can lead to high-pressure obstructed voiding patterns that can place a patient's upper tracts at risk. In addition, incontinence and reduced functional bladder capacity can greatly impair quality of life (QoL). Current frontline treatments for NDO using anticholinergic medications are of only modest benefit and fraught with intolerable side effects such as dry mouth and constipation as well as concerns on cognitive function [6].

Cruz et al. [11] published the first regulatory study examining the effect of onaBoNTA for NDO. A total of 275 multiple sclerosis (MS) or SCI patients who had inadequate response to or were intolerant to ≥1 anticholinergic medication were enrolled. These patients were randomized to receive onaBoNTA 200 U ($n$ = 92), onaBoNTA 300 U ($n$ = 91), or placebo ($n$ = 92). Results are presented comparing onaBoNTA 200 U to placebo since FDA regulatory approval was given for 200 U dose. By week 6, mean weekly urge incontinent episodes had decreased by 21.8 in the onaBoNTA 200 U group compared to a decrease of 13.2 in the placebo group ($p < 0.05$). The proportion of patients with a ≥50% reduction in weekly urge incontinence symptoms (i.e., clinically significant change) was significantly greater in patients receiving 200 U onaBoNTA vs. placebo (77.2% vs. 39.1%, respectively). In addition, full continence ("dry") was achieved in 38% of patients in the 200 U group compared to only 7.6% of placebo-treated patients ($p < 0.05$). Median duration of effect was 9–10 months in the onaBoNTA-treated group vs. 3 months in placebo-treated patients. No significant difference in efficacy was observed between 200 U and 300 U onaBoNTA groups. The main adverse events were urinary tract infections (UTIs) and urinary retention resulting in the need for clean intermittent catheterization (CIC). Urinary tract infection rates were similar across all treatment groups in SCI patients in whom 91.6% were using CIC at baseline. However, UTI rates in MS patients were linked not only with onaBoNTA dose but also with the need for CIC suggesting that initiation of CIC and not necessarily onaBoNTA itself was more responsible for the risk of developing a UTI. Overall, CIC was initiated in 12% of placebo patients, 29.5% of 200 U onaBoNTA, and 42.2% of 300 U onaBoNTA-injected patients.

Ginsberg and colleagues reported on the second large phase 3 trial in MS and SCI patients with NDO who received either placebo ($n$ = 149), onaBoNTA 200 U ($n$ = 135), or onaBoNTA 300 U ($n$ = 132) [17]. Mean weekly urinary incontinence (UI) episodes decreased by 21 in the onaBoNTA 200 U group compared to a decrease of 9 in the placebo group ($p < 0.05$). In addition, 75% of onaBoNTA 200 U group achieved a 50% or greater reduction in weekly UI episodes compared to 38% in the placebo group. Moreover, a significantly larger proportion of onaBoNTA 200 U-treated patients were fully continent following treatment compared to placebo-injected patients (i.e., 36% vs. 10%, respectively). The mean increase in maximum cystometric capacity was 151 ml in the onaBoNTA 200 U group compared to an increase of 16 ml in placebo patients. Maximum detrusor pressures were reduced by 69% in the onaBoNTA 200 U group vs. 9.5% in the placebo-treated patients. The median duration of effect was similar to the earlier trial of Cruz and colleagues (i.e., 8–9 months in the onaBoNTA 200 U group vs. 3 months in the placebo group). The main adverse events were UTIs and the need for CIC. CIC rates showed a dose-dependent response to onaBoNTA injection (i.e., placebo 10%, onaBoNTA 200 U 35%, onaBoNTA 300 U 42%). However, the need for CIC did not negatively impact clinical outcomes as improvements in quality of life (I-QoL) scores were similar in patients with or without the need for CIC. UTI rates were similar in all SCI groups but were higher in MS patients treated with onaBoNTA and presumably related to the concurrent increased need for CIC with onaBoNTA

injection. Muscle weakness was seen in 7 patients treated with onaBoNTA 300 U and 4 patients each in placebo and onaBoNTA 200 U groups. No neutralizing antibodies against onaBoNTA were observed after treatment.

Denys et al. [12] reported the efficacy and safety of two administration modes of bladder injection of abobotulinumtoxinA (aboBoNTA) 750 U in patients suffering from refractory NDO in a randomized placebo-controlled phase 2 study. Forty-seven MS or SCI patients were treated with 15 or 30 bladder injections of aboBoNTA 750 U or placebo. The primary end point was the change from baseline in the mean number of daily incontinence episode frequency (IEF) at 12 weeks. In both injection groups, the mean decrease in IEF was greater in the aboBoNTA-treated vs. placebo groups but it did not reach statistical significance ($p > 0.05$). However, increases in maximum cystometric capacity and reduction in maximum detrusor pressure were significantly greater in both aboBoNTA groups compared to their respective placebo groups. No difference in effect was observed between the two injection groups of aboBoNTA. Thus, the authors concluded that reduction to 15 injection sites did not appear to be associated with any impact on efficacy.

## *Repeated Injections*

Kennelly and colleagues reported on the results of an open-label 3-year extension of the phase III trial of onaBoNTA for NDO [22]. Three hundred ninety-six patients entered the extension study, and 68 patients received six injections over a 4-year period. The authors showed persistent benefits of onaBoNTA 200 U with time. The mean reduction in UI episodes/day ranged from 3.2 to 4.1 over all six injections. Between 83.2% and 91.3% of patients demonstrated ≥50% reduction in UI episodes and between 43.4% and 55.6% of patients were totally continent after treatment 1–6. The incidence of UTIs ranged from 14.3% to 27.6% and the finding of urinary retention varied between none and 20.2%. Both UTI and urinary retention risk decreased with each treatment cycle. In addition, onaBoNTA was shown to be a durable treatment as the duration of response remained steady at 9 months following injection. Table 15.1 summarizes the results of NDO trials using onaBoNTA.

**Table 15.1** Effect of OnaBoNTA in reducing urinary incontinence in NDO patients

| Author | Trial type | ≥50% reduction in UI episodes | 100% reduction in UI episodes |
|---|---|---|---|
| Cruz et al. [11] | Phase III | 77% | 38% |
| Ginsberg et al. [17] | Phase III | 75% | 36% |
| Kennelly et al. [22] | Open-label 3-year extension | 83–91% | 43–56% |

*OnaBoNTA* onabotulinumtoxinA, *UI* urinary incontinence, *NDO* neurogenic detrusor overactivity

## Overactive Bladder

Overactive bladder (OAB) is defined as urinary urgency, with or without urge urinary incontinence (UUI), usually accompanied with urinary frequency and nocturia [3]. The prevalence of OAB in the general population is 12–17%, and about half of OAB patients have incontinence [35]. The current guidelines for the management of OAB lists first- and second-line therapies as behavioral therapies and pharmacotherapy, respectively [18]. A meta-analysis of several RCTs of different anticholinergic drugs used for the treatment of OAB demonstrated improvements in both symptoms and QOL [8]. Unfortunately, most individuals discontinue anticholinergic therapy because of either inadequate long-term efficacy and/or intolerable side effects.

Nitti and colleagues presented results from the first phase 3 trial in 557 patients with refractory idiopathic OAB randomized to receive either onaBoNTA 100 U or placebo bladder injections [27]. At 12-week follow-up, the investigators found that patients receiving onaBoNTA had a 47.9% reduction in mean daily urge incontinence episodes vs. a 12.5% reduction in placebo-treated patients. Moreover, 57.9% of patients injected with onaBoNTA had ≥50% reduction in their urge incontinence symptoms and 22.9% were totally continent, compared to 28.9% and 6.5%, respectively, in the placebo group. The most common adverse events were UTIs (15.5% in the onaBoNTA group vs. 5.9% in the placebo group) and incomplete emptying resulting in the need for CIC (6.1% in the onaBoNTA group vs. 0% in the placebo group). The duration of CIC was less than or equal to 6 weeks in 59% of patients.

Improvements in other symptoms of overactive bladder, daily frequency of urination, and the amount of urine voided also occurred with onaBoNTA treatment compared to placebo at week 12. A second European-based randomized clinical trial in 548 patients comparing onaBoNTA 100 U to placebo showed comparable results [9]. At 12 weeks following injection, onaBoNTA-treated patients had a significantly greater reduction in daily incontinence episodes compared to the placebo group (53.1% vs. 16.8%). The most common adverse events were UTIs and the need for CIC demonstrated in 20.4% and 6.9% of onaBoNTA patients, respectively, compared to 5.2% and 0.7% of placebo-treated patients, respectively (Table 15.2).

**Table 15.2** Incidence of most frequent adverse events in NDO and OAB randomized trials

| Author | Patient type | Dose of onaBoNTA(U) | UTI (%) | CIC (%) |
|---|---|---|---|---|
| Cruz et al. [11] | NDO | 200 | 28 | 30 |
| Ginsberg et al. [17] | NDO | 200 | 28 | 35 |
| Nitti et al. [27] | OAB | 100 | 16 | 6 |
| Chapple et al. [9] | OAB | 100 | 20 | 7 |

*OnaBoNTA* onabotulinumtoxinA, *UTI* urinary tract infection, *CIC* clean intermittent catheterization, *NDO* neurogenic detrusor overactivity, *OAB* overactive bladder

## *Repeated Injections*

Durable efficacy and safety of onaBoNTA was demonstrated in a 3-year open label extension trial of two initial phase 3 randomized trials [28]. Four hundred thirty patients completed the 3-year extension study, and 33 patients received 6 treatments with onaBoNTA 100 U. The decrease in mean daily urge incontinence episodes ranged from 3.1 to 3.8 after each treatment with a median duration of effect of 7.6 months. Treatment duration greater than 12 months was seen in 28.5% of patients. The need for CIC was 4% after the first treatment cycle but this number decreased with each subsequent treatment cycle. No patient experienced seroconversion after receiving the 100 U dose. Patients with diabetes mellitus treated with onaBoNTA were twice as likely to develop urinary retention and require CIC. The most frequent adverse events of NDO and OAB trials using onaBoNTA are summarized in Table 15.2.

## *Comparative Trial*

The U.S. National Institute of Health sponsored a comparative study between onaBoNTA vs. neuromodulation [4]. For this study, conducted at nine centers, only women with refractory urgency urinary incontinence were randomized to an injection of onaBoNTA ($n$ = 192) or sacral neuromodulation ($n$ = 189). Of the 364 women, mean age 63 years, the onaBoNTA group had a statistically significant greater reduction in a 6-month average number of episodes of urgency incontinence per day than did the sacral neuromodulation group (−3.9 vs. −3.3 episodes per day). There were no cases of urinary retention with sacral neuromodulation while onaBoNTA increased the risk of UTI, retention, and need for self-catheterization. Although subjects treated with onaBoNTA noted greater improvement for symptom bother and treatment satisfaction than neuromodulation, there was no significant difference for quality of life or for measures of treatment preference, convenience, or adverse effects. A more recent publication compared economic costs between these two treatment modalities at a primary time point of 2 years and secondary time point at 5 years [20]. In both cases, onaBoNTA 200 U was a more cost-effective treatment than sacral neuromodulation for urge urinary incontinence (Table 15.3).

**Table 15.3** Economic costs of onaBoNTA 200 U vs. two-stage neuromodulation in patients enrolled in ROSETTA trial [20]

| Treatment | 2-year economic cost | 5-year economic cost |
|---|---|---|
| OnaBoNTA | $35,680 | $7460 |
| Sacral neuromodulation | $36,550 | $12,020 |

*OnaBoNTA* onabotulinumtoxinA, *ROSETTA* Refractory overactive bladder: Sacral NEuromodulation vs. BoTulinum Toxin Assessment

## Pediatric Uses

### *Spina Bifida*

The most common use of BoNTA in pediatrics is in patients with spinal dysraphism. A recent multicenter study detailed results of onaBoNTA (98%) or aboBoNTA (2%) injections in 53 patients with spina bifida [21]. The investigators found improvements in compliance (9.9 cm/$H_2O$ to 16.3 cm/$H_2O$) and maximum cystometric capacity following BoNTA treatment although maximum detrusor pressure was not significantly reduced. One subcategory (poor bladder compliance without detrusor overactivity) showed no significant improvement in any urodynamic parameter following BoNTA treatment suggesting that the bladder dysfunction may be related to bladder fibrosis and more appropriately treated with bladder augmentation surgery.

### *Non-neurogenic DO*

Recent interest in use of onaBoNTA in the pediatric population has extended to non-neurogenic patients. Bayrak and colleagues demonstrated reductions in urinary frequency, urge incontinence, and increases in bladder capacity in patients with non-neurogenic detrusor overactivity [5]. Moreover, vesicoureteral reflux disappeared in 50% of patients and was reduced in 30% of patients following onaBoNTA injection. Patients with VUR had higher pretreatment detrusor contractile pressures and poorer compliance compared to patients without VUR.

## External Urinary Sphincter

There are one Class I and two Class II studies of BoNT in detrusor sphincter dyssynergia (DSD) [13–15]. In the Class I study, the effects of BoNT vs. placebo was studied on DSD in 86 patients with multiple sclerosis (MS) [15]. The study employed a single transperineal injection of onaBoNTA, 100 U in 4 mL normal saline, or placebo, into the striated sphincter with EMG guidance. A single injection of BoNT did not decrease residual urine volume in this group of MS patients. These findings differ from those in patients with spinal cord injury and may be due to lower detrusor pressures observed in patients with MS. The American Academy of Neurology recommends BoNT to be considered for DSD but recognizes the limited head-to-head comparisons of treatment options in DSD. Kuo [23] evaluated the effects of onaBoNTA urethral injection in 27 patients with idiopathic low detrusor contractility. Detrusor contractility recovered in 48% of those treated. Patients with normal bladder sensation combined with poor relaxation or hyperactive urethral sphincter

activity were most likely to respond to urethral injections with onaBoNTA. Complications of BoNT injection into the external sphincter are rare except for transient stress urinary incontinence. In 38% of patients, the therapeutic effect of restoring detrusor contractility lasted over 1 year.

## Pelvic Floor Injections

Ghazizadeh and Nikzad [16] injected 150–400 U of aboBoNTA into the levator ani of 24 women with refractory vaginismus. Symptoms significantly improved such that 75% of patients could have satisfactory intercourse. In contrast, a double-blind randomized clinical trial of onaBoNTA vs. saline in 60 patients with 2 years or more of chronic pelvic pain that received either onaBoNTA 80 U (20 U/ml) or normal saline injections into the puborectalis and pubococcygeus muscles [1] showed mixed results. After 26 weeks of follow-up, quality of life measures were improved in both the onaBoNTA and placebo groups, but the difference between onaBoNTA and placebo groups did not reach statistical significance.

However, the authors found a reduction in resting pelvic muscle tone in women injected with onaBoNTA compared to placebo ($p < 0.001$), and this translated into significant improvements in both dyspareunia ($p < 0.001$) and nonmenstrual pelvic pain ($p = 0.009$). Adelowo et al. [2] reported on their experience using onaBoNTA (100 U–300 U) in 29 women with chronic myofascial pelvic pain. In this retrospective study, the authors placed several onaBoNTA 10 U injections (total 300 U) into the pelvic floor muscles. Pain improvement was seen in 79% of patients at <6 weeks postinjection. After a median of 4 months from the first injection, 52% requested repeat onaBoNTA. Urinary retention (defined by PVR > 100 ml) and fecal incontinence resulted in 3 patients and 2 patients, respectively, and these AEs completely resolved. Larger placebo-controlled RCTs and patient-reported outcomes are needed to support the use of onaBoNTA for women with myofascial pelvic pain refractory to standard pelvic floor physical therapy.

## Benign Prostatic Hyperplasia (BPH)

Application of BoNT to treat BPH was reported by Maria et al. [25]. Thirty men with symptomatic BPH were randomized to receive either 200 U of onaBoNTA (n-15) or placebo saline injection ($n = 5$). OnaBoNTA 100 U in 2 ml of saline or saline alone in the placebo arm was injected into each lobe of the prostate through the perineum via a 22-gauge spinal needle with transrectal ultrasound guidance. Clinical improvement was evident after 1 month. The investigators noted that the American Urological Association symptom score, a common index for the assessment of BPH, decreased by 65% compared to baseline in the onaBoNTA patients ($p = 0.00001$). Also, maximum flow rate increased from 8.1 to 14.9 mL/sec with

onaBoNTA ($p = 0.00001$). There was no significant improvement in patients injected with saline alone. No urinary incontinence or systemic side effects were reported over the 18-month follow-up.

Chuang et al. [10] stratified drug treatment refractory BPH with either prostate size <30 grams or >30 grams and injected them with either 100 U onaBoNTA or 200 U onaBoNTA, respectively, via ultrasound-guided perineal injection. At 12 months, the percent improvements in International Prostate Symptom Score (IPSS), maximum flow rate, and post void residual urine volume were similar to those of Maria et al. [25], except that the percent shrinkage of prostate size was substantially smaller (13–19% vs. 61%). In 29% of men there was no change in prostate volume, yet 58% of these men still had a >30% improvement in IPSS, maximum flow rate, and post void residual urine volume, suggesting that onaBoNTA may relieve BPH symptoms by an effect on sensory nerve pathways rather than reducing the prostate size alone.

McVary et al. [26] performed a phase 2 multicenter, placebo-controlled, randomized clinical trial using a onaBoNTA 200 U to treat men with BPH and moderate lower urinary tract symptoms. The men had an IPSS of 14 or >, a maximum flow rate of 4–5 mL/sec, and a post void residual urine volume ≤200 ml; 315 men were randomized to either onaBoNTA 200 U ($n = 158$) or placebo ($n = 157$). The primary end point was the change from baseline in IPSS at week 12. Although a significant decrease from baseline in IPSS was seen with both onaBoNTA (−6.3 points) and placebo (−5.6 points), there was no difference between the groups; however, onaBoNTA showed efficacy over placebo in improving maximum flow rate at week 6 postinjection ($p \leq 0.01$). The most common adverse events in both groups were hematuria and hematospermia. The authors concluded that intraprostatic injection of onaBoNTA was not more efficacious compared to placebo in improving lower urinary tract symptoms and the commercial development of onaBoNTA for BPH indication was subsequently stopped at this time.

## Bladder Pain

Interstitial cystitis/bladder pain syndrome (IC/BPS) is defined as pain perceived to be related to the urinary bladder, associated with lower urinary tract symptoms greater than a 6-month duration, in the absence of infection or other identifiable causes [24]. The first report using BoNT as a therapeutic was a case series of 13 women with NIDDK-defined IC [33]. The patients underwent submucosal transurethral injections of 100–200 U of abobotulinumtoxinA (7 patients) or onaBoNTA 100 U (6 patients) into 20–30 sites in the trigone and bladder base. Validated questionnaire (Interstitial Cystitis Symptom Index, Interstitial Cystitis Problem Index) or voiding charts and a visual analog pain scale were evaluated at baseline, 1-month, and subsequently at 3-month intervals. Statistically significant improvements in frequency, nocturia, and pain were observed 1 month following treatment, with improvements in first desire to void and cystometric capacity in those patients so

evaluated. Onset of symptom relief was 5–7 days following treatment, and mean duration of symptom relief was 3.7 months. These results were supported by basic science experiments demonstrating that onaBoNTA reduces urothelial release of ATP in chronic bladder inflammation [34].

Kuo and Chancellor [24] performed a randomized trial in IC/BPS patients comparing bladder hydrodistention (HD) with either 100 U or 200 U doses of onaBoNTA vs. hydrodistention alone. At 3 months, the bladder pain visual analog scale, functional bladder capacity, cystometric bladder capacity, and global response assessment significantly improved only in the onaBoNTA groups vs. the control group. The 200 U dose did not provide better efficacy compared to 100 U, and there were more side effects, including urinary retention, with using 200 U onaBoNTA. These studies suggest a potential promising effect of botulinum toxin for treating bladder pain.

## Conclusion

The use of botulinum toxin for the treatment of neurogenic and refractory idiopathic overactive bladder has resulted in improved continence and quality of life. The intraprostatic injection of botulinum toxin for benign prostatic hypertrophy to date has not shown efficacy in improving lower urinary tract symptoms. Treating detrusor sphincter dyssynergia, myofacial pain, and interstitial cystitis/bladder pain syndrome with botulinum toxin have showed some promising results in controlled trials but they are currently an off-label use of the product. Application of botulinum toxin for lower urinary tract dysfunction is exciting, expanding, and evolving. We believe there will be further exciting advances in the application of botulinum toxin in the genitourinary system in the near future.

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