Botulinum Toxin Therapy for Voiding Dysfunction

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Introduction

Botulinum toxin is a neurotoxin which is produced by the gram-positive bacteria *Clostridium botulinum* and has been utilized therapeutically since the 1980s. Botulinum toxin exerts its effects at the presynaptic nerve terminals by inhibiting the release of the neurotransmitter acetylcholine. There are numerous subtypes of the toxin used in clinical practice; however the subtype most familiar to urologists and urogynecologists is onabotulinumtoxinA. Botulinum toxin is available in different commercial forms which are molecularly distinct and thus differ in their pharmacologic properties. As such, they are not interchangeable in terms of potency and dosage. Three readily available commercial products used globally include onabotulinumtoxinA (BOTOX®, Allergan, Inc., Irvine, CA, USA) (Fig. 17.1), incobotulinumtoxinA (Xeomin®, Merz Pharma GmbH & Co KGaA, Frankfurt am Main, Germany), and abobotulinumtoxinA (Dysport®, Ipsen Biopharmaceuticals, Inc., Basking Ridge, NJ, USA). The following chapter will discuss the use of onabotulinumtoxinA (BOTOX®) as it relates specifically to the field of urology and female pelvic medicine and reconstructive surgery.

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Mechanism of Action

Botulinum toxin is a molecule consisting of a heavy chain and a light chain which are bound by a disulfide bond. The heavy chain of onabotulinumtoxinA binds to the secretory vesicle protein SV2, which is active and exposed to the synaptic cleft during exocytosis [1] (Fig. 17.2). The molecule is then internalized by the process of receptor-mediated phagocytosis. The two chains' disulfide bonds are broken down, and the light chain is released into the neuron's cytosol where it disrupts the fusion of the presynaptic vesicles from releasing the neurotransmitter acetylcholine. Several proteins are involved in vesicle-mediated neurotransmission and collectively form the SNARE complex. OnabotulinumtoxinA specifically targets and cleaves the synaptosomal nerve-associated membrane protein 25 (SNAP-25), which ultimately defunctionalizes the protein complex. By the disruption of the SNARE complex, onabotulinumtoxinA prevents the docking of vesicles transporting acetylcholine to the nerve ending, therefore preventing its release into the synaptic cleft. Interestingly, both molecular targets for onabotulinumtoxinA, SNAP-25 and SV2, are located ubiquitously throughout the parasympathetic nerves [2, 3]. In the lower urinary tract, parasympathetic stimulation of the detrusor muscle by acetylcholine stimulation of M2–3 receptors is largely responsible for detrusor contraction (Fig. 17.3). Therefore, acetylcholine release inhibition by onabotulinumtoxinA is thought to contribute to the

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Fig. 17.1 OnabotulinumtoxinA 100 unit and 200 unit vials (BOTOX®). (Courtesy of Allergan, Inc., Irvine, CA, USA)

desired clinical effects (in the case of detrusor overactivity) of "calming" the contraction of the bladder.

OnabotulinumtoxinA also plays a role in modulating the handling of afferent stimuli in the bladder thought to be central to the pathophysiology of overactive bladder. This is accomplished by several pathways, one of which is onabotulinumtoxinA inhibiting the SNARE complex-dependent exocytosis of neuropeptides (substance P, CGRP) by the sensory nerves [4–8].

Additionally, onabotulinumtoxinA has been shown in rat models to inhibit purinergic transmission (stimulatory effect on the afferent nerves), while increasing nitric oxide release from the urothelial cells (inhibitory effect on the afferent nerves) [9]. Although evidence for these mechanisms is not as robust as the evidence supporting its role as a chemical denervating agent, clinical evidence with onabotulinumtoxinA bladder instillation has supported its effect on afferent pathways [10, 11].

Indications for Use of OnabotulinumtoxinA

Numerous medical conditions are treated with onabotulinumtoxinA, in addition to its applications in urology and female pelvic medicine (Table 17.1). Although there are several off-label uses for onabotulinumtoxinA in urology and female pelvic medicine, onabotulinumtoxinA is currently the only FDA approved for the use in adults for neurogenic detrusor overactivity (NDO) and non-neurogenic overactive bladder (OAB).

Use in Neurogenic Detrusor Overactivity (NDO)

Neurogenic detrusor overactivity (NDO) is a urodynamic observation characterized by involuntary detrusor contractions during filling cystometry in a patient with associated neuro-

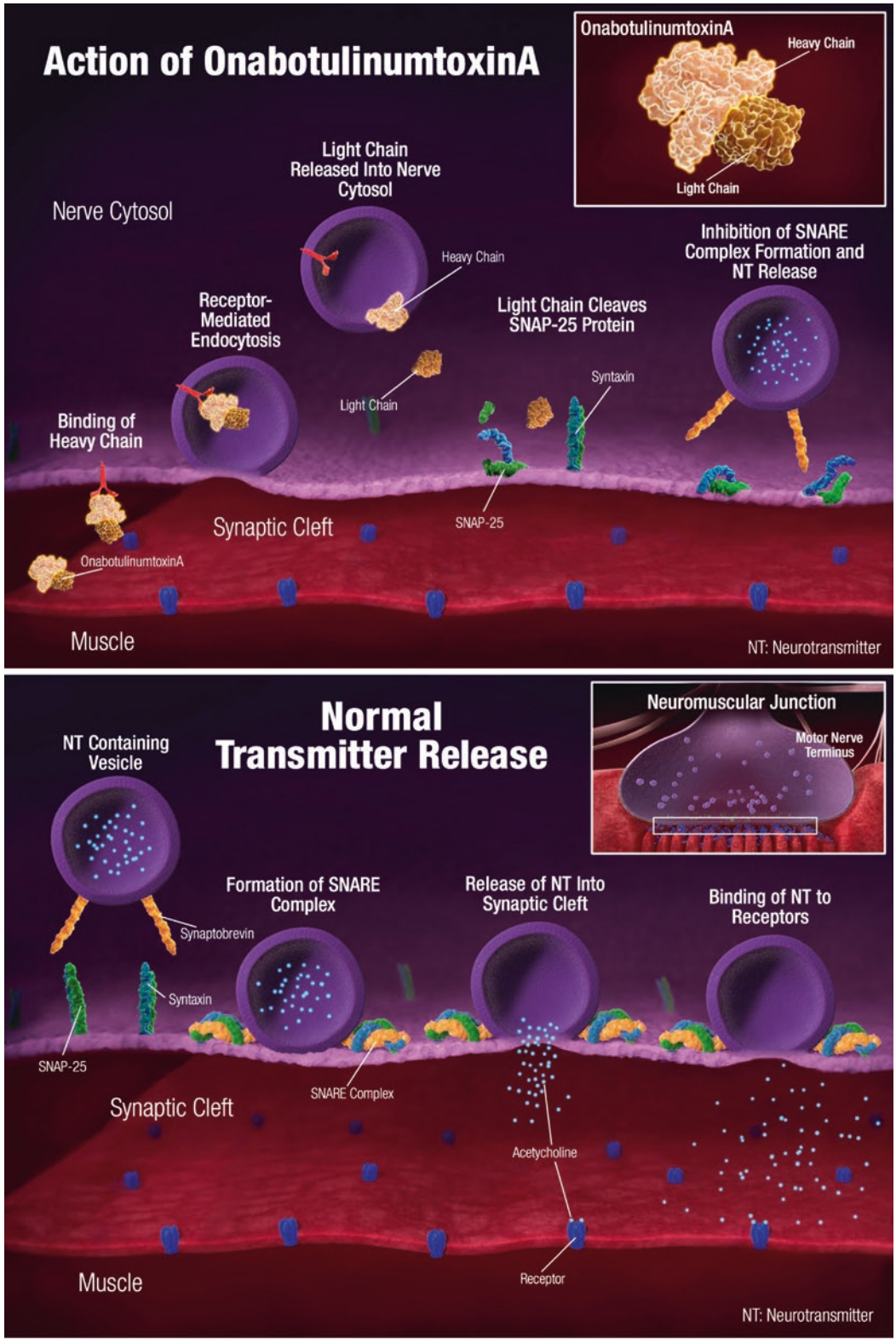

Fig. 17.2 Botulinum Toxin Mechanism of Action. (Courtesy of Allergan, Inc., Irvine, CA, USA)

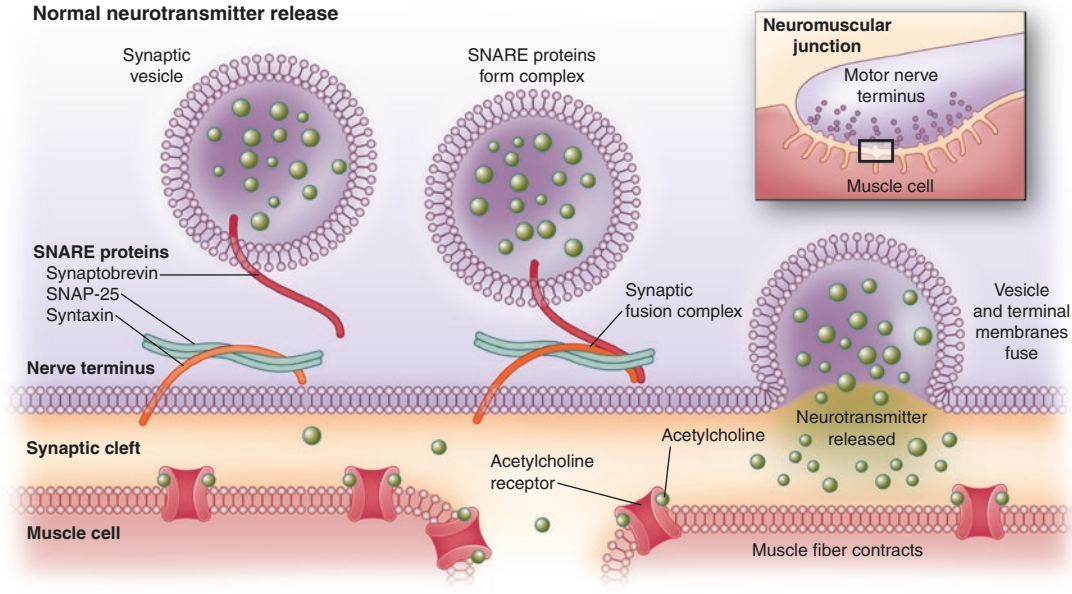

Fig. 17.3 Normal cholinergic-mediated neurotransmission at neuromuscular junction. (Courtesy of Allergan, Inc., Irvine, CA, USA)

Table 17.1 Approved conditions treated with onabotulinumtoxinA injection and recommended dosing

Condition	Dose (Units)[a]
Overactive bladder	100 U
Neurogenic detrusor overactivity	200 U
Chronic migraine	155 U
Upper limb spasticity	75–400 U[b]
Lower limb spasticity	300–400 U
Cervical dystonia	198–200 U
Axillary hyperhidrosis	100 U
Blepharospasm	3.75 U–7.5 U per affected eye
Strabismus	Variable[c]
Cosmetic	4–40 U

[a]One should not exceed injecting 400 units for any indication within a 3-month period

[b]Dose may vary depending on the muscle group injected and electromyographic (EMG) response

[c]Dose varies based on prism diopter correction and ongoing treatment response. Communication with treating physician is recommended as redosing occurs in up to half of patients

logical disease and plays a central role in the development of adult neurogenic lower urinary tract dysfunction (NLUTD) [12]. This observation is thought to be responsible for the bothersome lower urinary tract symptoms experienced by patients with various neurological diseases and includes urinary urgency, urgency urinary incontinence (UUI), frequency, and nocturia. Common neurological conditions that are associated with NDO include multiple sclerosis (MS), spinal cord injury (SCI), Parkinson's disease, and cerebrovascular accident. Up to 52% of patients with SCI or MS have urgency urinary incontinence. NDO and the associated urinary incontinence may play a deleterious role in a patient's quality of life and preservation of hygiene [13, 14]. Initially one may consider behavioral therapy in the treatment plan; however many patients will require additional forms of therapy including oral pharmaceuticals, clean intermittent catheterization (when incomplete bladder emptying is also present), botulinum toxin injection, and urinary diversion in more severe cases [15].

Initial pharmacologic therapy for patients with NDO includes anticholinergic therapy with oral medications that preferentially competitively antagonize muscarinic receptors in the bladder [15]. Various anticholinergic medications have been used to treat patients with NDO, as there is no conclusive evidence to suggest one medication over the other. However, oxybutynin is FDA

approved in pediatric patients with NDO. In general, most patients with neurogenic bladder will need high doses of anticholinergic medications in order to achieve the greatest therapeutic benefit [16, 17]. As a result, these patients may experience high rates of bothersome side effects associated with this class of medications, namely, xerostomia (dry mouth), constipation, and central nervous system-related side effects (i.e., dizziness, cognitive impairment). As is common with other medications, drug efficacy is reliant upon adherence to therapy. Various studies have investigated that drug compliance is poor with antimuscarinic therapy for idiopathic overactive bladder, and thus one must consider a similar problem in the neurogenic population [18, 19]. Alternatively, clinicians may consider the use of a beta 3 agonist for initial or second-line oral pharmacotherapy in patients with NDO. In a recent prospective, randomized, double-blind placebo-controlled study by Krhut et al., patients with SCI and MS were randomized to mirabegron 50 mg or placebo. A total of 66 patients were included in the study and the authors reported significant increases in bladder compliance, cystometric capacity, and reduced leakage as measured by a pad weight test [20]. Furthermore, patients in the treatment arm experienced a low risk of adverse effects when compared to the placebo group (6.25% v. 2.94%). These results are promising for patients with NDO; however, data are still limited. If side effects are not tolerated/acceptable or efficacy is inadequate with oral medication then one considers more advanced therapies.

The first published report on the use of onabotulinumtoxinA in the urinary tract was put forth by Dykstra et al. in 1988, where the toxin was used to treat detrusor sphincter dyssynergia in patients with spinal cord injuries [21]. After a successful nonrandomized trial using intradetrusor botulinum toxin in SCI patients, Schurch et al. published their results from the first phase 2 randomized, double-blind, placebo-controlled trial utilizing onabotulinumtoxinA injections in the bladder [22, 23]. The group randomized 53 patients with SCI and 6 with MS to receive 200 U or 300 U of onabotulinumtoxinA or placebo. Patients were followed clinically up to 24 weeks including urodynamic studies occurring 2 weeks prior to injection and then at 2, 6, and 24 weeks postinjection. Comparable to their initial trial, the investigators found significant improvements in urodynamic parameters including increased mean cystometric capacity (174 mL in 200 U group, 92 mL in 300 U group), increased reflex detrusor volume (volume at first involuntary detrusor contraction; of note, 23 patients did not demonstrate involuntary detrusor contraction on at least one follow-up visit), and decreased mean detrusor pressure during involuntary detrusor contractions (−38 cmH_2O for 200 U; − 35 cm H_2O for 300 U). Of note, the changes in baseline in cystometric capacity were higher than the placebo group at every follow-up interval with the exception of 24 weeks in the 300 U cohort. Most importantly, the investigators found that both treatment groups had significant improvements in incontinence episodes, and 49% of the treatment group (14 patients in 200 U and 10 patients in 300 U group) reported resolution of incontinence for at least 1 week. Furthermore, clean intermittent catheterization (CIC) rates remained constant throughout the study period and comparable to placebo [23]. One limitation of this study is that no clear difference between 200 U and 300 U injections was demonstrated. Subsequently, Hershorn et al. performed a multicenter phase 2 randomized, placebo-controlled trial also demonstrating efficacy in reducing incontinence episodes and improving quality of life in patients with NDO [24].

Two multicenter, placebo-controlled, phase 3 randomized controlled trials spearheaded by the DIGNITY (Double blind InvestiGation of purified Neurotoxin complex In neurogenic detrusor overactivitY) clinical research program solidified the evidence in support of the use of onabotulinumtoxinA for NDO and ultimately led to FDA approval [25, 26]. Both trials included patients with urodynamically proven NDO and a history of SCI or MS. Inclusion criteria for SCI were a history of an injury occurring at T1 and below at least 6 months prior to screening. MS patients screened had to score ≤6.5 on the Expanded Disability Status Score (the ability to walk must

be demonstrated) [25–29]. The primary endpoint for both studies was the degree in change in weekly urinary incontinence episodes from baseline to week 6. Secondary endpoints included changes in Urodynamics, Quality of Life, and adverse effects. In 2011, Cruz and colleagues performed a multi-institutional double-blind randomized controlled trial comparing 200 U and 300 U of onabotulinumtoxinA to placebo in a cohort that included 154 patients with MS and 121 patients with SCI [25]. Patients in the treatment arm had statistically significant decreases in urgency incontinence episodes as noted on 7-day bladder diaries in both the 200 U (−21.8. incontinent episodes) and 300 U (−19.4 incontinent episodes compared to placebo). Furthermore, patients in the study achieved significant dry rates in comparison to patients in the placebo arm when stratified by underlying neurological condition and dose [MS, 43%, 200 U; 41%, 300 U; SCI, 31% for 200 U, 37% for 300 U]. The study also reported on rates of urinary tract infection (UTI) and urinary retention. UTI incidence was similar across all groups in the study (placebo, 200 U, and 300 U) in the SCI population, while patients in the MS population UTIs were more common in the patients receiving onabotulinumtoxinA injections. Although the rate of UTI was high (53% for placebo, 60% for treatment group), the study did not distinguish between symptomatic and asymptomatic infections. Furthermore, roughly half of patients included in the study were performing clean intermittent catheterization (CIC) upon recruitment (52% overall, 50% in treatment group) contributing to a high rate of bacteriuria that was regarded as a UTI. Urinary retention requiring CIC increased with treatment dose (12% placebo, 30% 200 U, 42% 300 U in the first treatment cycle) and was initiated at the treating physician's discretion which may have led to higher rates of CIC than would be seen in clinical practice.

In 2012 Ginsberg et al. reported on the second trial for DIGNITY which included 416 patients, of which 227 had MS and 189 had SCI [26]. Both treatment groups achieved a statistically significant reduction in incontinent episodes documented on a 7-day bladder diary (−21 episodes for 200 U, −23 episodes for 300 U), and a significant number of patients were reportedly dry by week 6 (36% of 200 U cohort, 41% of 300 U cohort). Urodynamic diagnoses and quality of life also improved significantly in treatment groups in comparison to placebo [26]. Adverse effects were similar to the prior phase 3 trial by Cruz and colleagues, notable for de novo CIC in 35% of patients receiving 200 U and 42% receiving 300 U. UTI was the most common adverse effect, but as was observed in the aforementioned study this must be interpreted within the context of the patient population. For example, patients in the placebo arm with a history of SCI had a UTI rate of 42%, while 50% of the SCI patients with active treatment developed UTI. The high rate of UTI in this group is reflective of the prevalent use of CIC in this population. Furthermore, in the MS patient population approximately 50% of the treatment arm developed UTI in comparison to 28% of patients in the placebo arm. This, however, was likely driven by de novo incomplete bladder emptying requiring CIC and how the investigators defined "UTI." For example, applying the definition described in the study, patients developing asymptomatic bacteriuria after beginning a CIC regimen would be considered to have a UTI regardless of symptoms and subsequently influence this adverse event's rate. Data from both of these pivotal trials have been pooled by Ginsberg et al. who found significant differences in the reduction of urinary incontinence episodes, improvements in urodynamic parameters (increased cystometric capacity, reduction in detrusor pressure during involuntary detrusor contractions), improved quality of life, and patient satisfaction with both treatment doses. Interestingly, no significant difference in reduction of urinary incontinence episodes or dry rate was noted between 200 U and 300 U injections. Despite similar improvements in incontinence between both treatment doses, patients receiving 300 U injections did have a higher rate of urinary retention as well as a statistically significant difference in satisfaction after initiating CIC [30]. In addition to reporting the aforementioned common adverse events, there were no reports of respiratory compromise, MS

exacerbation, and development of neutralizing antibodies to the injected toxin.

Long-term data for onabotulinumtoxinA in NDO were reported by Kennelly et al. who published the results of a multicenter prospective trial recruiting 396 patients who had completed 1 year of the phase 3 randomized controlled trials [31]. The endpoint was the change in the mean number of incontinence episodes per week, 6 weeks after each injection. Initially patients were randomized to placebo, 200 U, and 300 U injections; however after FDA approval in 2011, all patients in the treatment arm received 200 U. Over the 4-year treatment period, daily incontinence episodes decreased (−3.2 to −4.1 per day in 200 U group) while 43–56% of patients were dry across six treatments. Similarly, the majority of patients reported greater than 11-point increases in the I-QOL (incontinence quality of life) questionnaire score, and this was consistent across time. In terms of adverse effects, de novo CIC use was 29.5% after the first treatment, while this number dropped to 3.4% with the second injection. Another important observation made in this study is the small percentage of patients who developed antibodies; 2.1% of patients were enrolled. Interestingly, the patients who developed antibodies were retreated sooner than their counterparts, undergoing repeat injection at a mean of 5 months (4 months sooner than median retreatment time or 9 months) [31]. Other groups have also reported on the long-term use of onabotulinumtoxinA including Joussain and colleagues who performed a retrospective study including 292 patients with MS, SCI, and spina bifida [32]. Their primary endpoint was failure and withdrawal rate at intervals of 3, 5, and 7 years after the initial treatment. After 3 years, 80% of the cohort continued treatment, while 71% and 60% continued treatment after 5 and 7 years, respectively. Overall the treatment remained safe throughout the study period, but one case of pseudo-botulism was reported. Leitner and colleagues also reported on the long-term use of onabotulinumtoxinA in patients with NDO [33]. Their cohort consisted of 52 patients with SCI, MS, or spina bifida who had begun onabotulinumtoxinA treatment over 10 years prior to publication. They found that despite having a 40% discontinuation rate, as one could expect over an extended follow-up period, treatment efficacy was maintained after multiple repeat injections. Of the patients who discontinued treatment, half were patients who did not respond clinically and/or urodynamically. Three patients (all had SCI) developed antibodies to onabotulinumtoxinA, which occurred after the 4th, 7th, and 8th injections.

Approximately 32% of patients with NDO fail to respond to onabotulinumtoxinA injection [34]. This presents a treatment dilemma to patients and physicians alike as alternatives, such as urinary diversion, may be undesirable options. Peyronnet et al. performed a retrospective study comparing repeated use with the same toxin versus using a different botulinum toxin A after a patient had failed to respond [35]. For patients who had received onabotulinumtoxinA initially, they were switched to receive 750 U abobotulinumtoxinA. If patients received 750 U abobotulinumtoxinA, they were switched to 200 U onabotulinumtoxinA. The authors noted a successful result in 51% of patients who had a switch, in comparison to 24% success in those who remained on the same dose and toxin. A similar study by Bottet and colleagues studied a cohort of 57 onabotulinumtoxinA failures which were all switched to 750 U abobotulinumtoxinA [36]. The authors found significant improvements in daily incontinence episodes in 52% and improved urodynamic parameters (cystometric capacity and reduction in maximum detrusor pressure) in all patients. Most importantly, 87% of patients who were switched to 750 U abobotulinumtoxinA continued to have a therapeutic response after 21-month follow-up, suggesting a long-term option for nonresponders. Although these early studies show promising results for abobotulinumtoxinA, ongoing research is underway and contributes to the growing body of evidence showing its benefits in this population [37].

Although most large trials investigating the use of onabotulinumtoxinA for NDO included patients with MS, SCI, or myelomeningocele, one must note that this therapy may be used

successfully for voiding dysfunction associated with other neurological conditions [38]. One particular example is Parkinson's disease (PD). Approximately half of PD patients may experience urgency urinary incontinence in addition to bothersome storage symptoms (urgency, frequency, nocturia) and obstructive lower urinary tract symptoms [39]. Botulinum toxin injection in PD has been studied in several small series with success in treating urgency incontinence and a relatively low rate of urinary retention (0–12.5%) [40–45]. Given the lack of randomized controlled trials in the literature, there is a paucity of data in the best dosing regimen for patients with PD. Despite this limitation, onabotulinumtoxinA has the potential to alleviate symptoms associated with NDO and carries little to no risk of interacting with medications being administered for PD (particularly anticholinergics).

In conclusion, patients with NDO resulting in adult neurogenic lower urinary tract dysfunction (ANLUTD) may be treated successfully with intradetrusor onabotulinumtoxinA injections. Treatment may result in significant improvements in urinary urgency, urgency urinary incontinence, and improvements in quality of life. Although repeated injections are necessary, efficacy is maintained during the treatment course and alternatives are being investigated for those patients with suboptimal response.

Use in Overactive Bladder

Overactive bladder is a condition characterized by urinary urgency, with or without UUI, urinary frequency, and nocturia [46]. Approximately 16% of the US population is affected by this condition, and about 1/3 of patients affected by this condition have associated urgency urinary incontinence [47]. Furthermore, the prevalence is expected to continuously increase, reaching 20% prevalence by 2018 [48]. Patients with OAB are usually treated in a stepwise fashion as suggested by the AUA/SUFU (American Urological Association/Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction) guideline for OAB in adults [49]. These steps are referred to as first-, second-, and third-line therapies. First-line therapies consist of behavioral therapies (i.e., pelvic floor exercises, diet/fluid manipulation), and pharmacologic therapies form the mainstay of second-line treatments (although they may be introduced along with behavioral therapies). Oral pharmacologic options consist of antimuscarinic medications and oral beta 3 receptor agonists. Although both medication classes have been shown to be effective in treating OAB symptomatology and improving quality of life, they are limited by poor long-term persistence on the medication regimen. Studies suggest most patients discontinue therapy with beta 3 agonists or antimuscarinic medications 1 year after initiating therapy (62% and 80%, respectively) [18, 50, 51]. For patients who are refractory to first- and second-line therapies and/or cannot tolerate medication side effects, intradetrusor onabotulinumtoxinA injection is considered a "standard" third-line therapy in the appropriately counseled patient [49].

Initial small series composed of noncontrolled and randomized placebo-controlled studies were performed to demonstrate the efficacy of botulinum toxin injection for OAB [52–55]. Two subsequent phase 2 multicenter, randomized controlled trials assessed the safety and efficacy of various dosing ranges and compared them to placebo [56, 57]. Both studies included patients with refractory OAB with eight or greater UUI episodes daily. Dmochowski et al. utilized 50, 100, 150, 200, and 300 U injections of onabotulinumtoxinA, whereas Denys et al. utilized 50, 150, and 200 unit onabotulinumtoxinA injections. Both studies found substantial improvements in UUI for injections greater than 100 U; however doses higher than this were observed to place patients at additional risk of incomplete bladder emptying requiring CIC.

Two multicenter randomized controlled trials investigated the use of 100 U of onabotulinumtoxinA in patients with idiopathic OAB [58, 59]. Nitti et al. investigated the use of a 100 U dose of intradetrusor onabotulinumtoxinA injection in patients with refractory OAB versus placebo [58]. Included patients had a baseline of 3 or

more UUI episodes over a 3-day period and 8 or more voids daily. Patients included also needed to discontinue their anticholinergic medications and demonstrated adequate bladder emptying (PVR <100 mL). Follow-up occurred regularly (2, 6, 12 weeks, then every 6 weeks) until study exit at 24 weeks. If patients had greater than 2 incontinent episodes in a 3-day period or requested a repeat injection at the 12-week interval, they were offered retreatment. Outcome measures included daily UUI episodes, positive response to treatment benefit scale (TBS) at 12 weeks, number of voids, and urgency episodes. The investigators found that onabotulinumtoxinA injection produced a statistically significant difference in the reduction of daily UUI episodes when compared to placebo (2.65 v. 0.87, $p < 0.001$) and significant positive response on TBS which was sustained from week 2 to 12 (60.8% with positive response at week 12 v. 29.2%, $p < 0.001$). Furthermore, patients receiving onabotulinumtoxinA injection benefited from a significant reduction in OAB symptoms including urgency, number of daily voids, and nocturia. Total continent rates ("dry rate") were also affected by botulinum toxin injection and approximately 23% in the onabotulinumtoxinA group and 6.5% in the placebo arm were dry at the completion of the study. Quality of life improvements as measured by I-QOL and King's Health Questionnaire (KHQ) also favored patients in the onabotulinumtoxinA group versus placebo. The most common adverse effects were UTI (24.5% onabotulinumtoxinA v. 9.25% placebo) and incomplete bladder emptying requiring CIC (6.1% onabotulinumtoxinA v. 0%). Of note, the number of patients who developed UTI increased in both groups from 12 weeks to 24 weeks, likely reflecting the inherent risk in developing UTI when instrumenting the urinary tract. Interestingly, only one additional patient required CIC after 12 weeks. Chapple and colleagues used a similar study protocol in Europe and found a comparable decrease from baseline UUI in patients undergoing onabotulinumtoxinA injection versus placebo at 12 weeks (−2.65 v. 1.03, $p < 0.001$) [59]. Improvements following injection were also reflected by 62.8% of patients reporting a positive treatment response on TBS scale. The most common adverse effects were also echoed in this study, with UTI (24% onabotulinumtoxinA v. 9.6% placebo) and incomplete bladder emptying requiring CIC (6.9% onabotulinumtoxinA v. 0.7% placebo) being reported at similar rates. Of note, both trials' CIC threshold dictated that patients with a PVR greater than 350 mL begin CIC or those with symptoms of incomplete bladder emptying and a PVR of 200–350 mL. Other groups have used less stringent CIC guidelines safely and found a de novo CIC rate as low as 1.6% [60].

Sievert and colleagues performed a pooled analysis of both of the aforementioned trials [61]. This group found a statistically significant reduction in UUI episodes in the treatment arm compared to placebo (−2.8 v. −0.95, $p < 0.001$) as well as decreased number of daily voids and urgency episodes. Furthermore, the dry rate significantly favored the treatment arm compared to placebo (27.1% v. 8.4%, $p < 0.001$). Furthermore, a systematic review and meta-analysis performed by Ramos and colleagues focused primarily on randomized placebo-controlled trials also found significant reductions in UUI, urgency, and number of micturitions for patients treated with onabotulinumtoxinA [62]. Overall, there are robust level one data in support of using onabotulinumtoxinA injections for OAB.

Long-term follow-up was also reported by Nitti and colleagues for patients who completed one of the phase 3 randomized controlled trials [63]. This was an open-label extension study that concluded after 3.5 years or 6 treatment cycles. A total of 839 patients enrolled in the study and 829 patients received 1 or more onabotulinumtoxinA injections. Patients were permitted to request for retreatment in order to replicate daily clinical practice (retreatment criteria: PVR <200 mL, ≥2 episodes UUI in 3 days, ≥12 weeks since last injection). After a 3.5-year study period, 51.3% of patients completed the study and significant reductions in daily UUI episodes were sustained in both the overall population and subgroups corresponding to number of treatments the patient received (−3.1 to 3.8 in overall population; −2.9 to −4.5 in individual subgroups). Similarly,

overactive bladder symptoms and quality of life were significantly improved, while patient satisfaction remained high as measured by the TBS. Overall the median time to retreatment was 7.6 months, and almost a third of patients had sustainable effects up to 1 year. Of the patients who withdrew from the study, only 5.7% of patients reported lack of efficacy and 5.1% reported bothersome side effects. Most patients who withdrew during the study period reported personal reasons, study burden, and site closure impeding their participation in the study. This long-term study also clarifies concerns over long-term adverse events including UTI, urinary retention, and antibody formation. Overall there were no changes in adverse effects with each additional treatment, for example, the development of UTI ranged between 13.5% and 17.5% of patients. The study protocol dictated that CIC be initiated if PVR was >350 mL regardless of symptoms or 200–350 mL with symptoms of incomplete bladder emptying. After the first injection, merely 4% of patients required CIC which decreased with each subsequent injection. There were no patients developing toxin neutralizing antibodies when receiving 100 U of onabotulinumtoxinA; however 3 patients developed antibodies after receiving 150 U (this part of the protocol was amended in 2012). Overall, this study provides support for the use of onabotulinumtoxinA as a suitable long-term option for OAB patients who are refractory to first- and second-line therapies.

Few studies have compared intradetrusor onabotulinumtoxinA injections to oral second-line therapies for OAB. One study by Drake and colleagues used a method known as network meta-analysis in order to compare treatments for OAB using data from published clinical trials [64]. They included studies evaluating the efficacy of onabotulinumtoxinA, mirabegron, and several anticholinergics used in clinical practice. Their results showed that all of the interventions were more efficacious than placebo in multiple outcomes studied (urgency incontinence episodes, micturition, and urgency episodes) at 12 weeks. OnabotulinumtoxinA showed the greatest reduction in all OAB symptoms investigated. Furthermore, onabotulinumtoxinA had the highest odds in achieving 100% resolution of UUI as well as the greatest mean reduction in urgency incontinence episodes and micturition and urgency episodes when comparing the treatments with each other. Despite the ability to compare a large number of trials and interventions, using network meta-analysis is subject to certain limitations inherent to the biases and quality of the studies included. Visco and colleagues performed a multicenter randomized controlled trial comparing the oral anticholinergic solifenacin with a single injection of onabotulinumtoxinA [65]. A study population composed of women with ≥5 UUI episodes (recorded on 3-day diary) was randomized to a cohort receiving oral solifenacin and a placebo injection (normal saline) or a second group receiving 100 U of onabotulinumtoxinA and placebo oral medication. Patients in the oral anticholinergic arm were started at 5 mg of solifenacin; however dose escalation to 10 mg could occur at 2 months. Additionally, patients in this arm could also change medication to trospium 60 mg daily if their symptoms were refractory to oral solifenacin by 4 months. After a 6-month follow-up, the authors concluded there was similar reduction in UUI episodes when comparing the patients receiving oral anticholinergics versus onabotulinumtoxinA. More patients in the onabotulinumtoxinA group enjoyed complete resolution of UUI (27% v. 13%, $p = 0.003$); however they also had higher rates of UTI (33%) and incomplete bladder emptying (5%).

Few well-designed studies are available that compare botulinum toxin injection to sacral neuromodulation. Recently, investigators for the ROSETTA trial reported their outcomes when comparing onabotulinumtoxinA injection and sacral neuromodulation for women who had refractory urgency urinary incontinence [66]. Eligible patients were randomized to receive 200 U onabotulinumtoxinA injection (higher than the FDA-approved dose for idiopathic OAB), and a second group was randomized to undergo sacral neuromodulation. Furthermore, only the patients who had greater than a 50% improvement in the onabotulinumtoxinA group were compared to the patients who underwent

stage 2 sacral neuromodulation implantation. After a period of 6 months, the patients in the onabotulinumtoxinA group had a greater mean reduction in incontinence episodes (−3.9 v. −3.3), as well as a higher rate of complete resolution of urgency urinary incontinence (20% v. 4%). Despite the greater reduction in incontinence episodes in the botulinum toxin group, there was no difference in the patient's overall perception in overall improvement; thus it is unclear whether this improvement is clinically relevant.

Patient Selection and Workup

Patients who are considered for intradetrusor onabotulinumtoxinA injection are typically refractory to initial therapies for NDO and OAB [49]. However, patient treatment plans should be individualized to optimize convenience for the patient, compliance with therapy, minimize side effects, and optimize quality of life. In addition to considering the patients' lower urinary tract condition, one must consider the patients' overall medical condition, current medications, and a realistic assessment of goals of therapy.

In patients refractory to first- and second-line therapies including behavioral modification and oral medications (antimuscarinics and beta 3 agonists), a detailed history and physical examination should be performed in order to select the appropriate third-line therapy and screen for contraindications to receiving onabotulinumtoxinA injections (Table 17.2). When obtaining a history, it is critical to ask specifically about the duration of prior treatments, side effects experienced, and whether dose escalation was attempted. Furthermore, modifiable behaviors and fluid intake should be addressed prior to considering injection with onabotulinumtoxinA (i.e., excessive caffeine). In patients referred with refractory OAB, details about previous therapies the patient has tried should be obtained. Details about duration of therapy, medication dose and frequency, and side effects encountered should be obtained from the patient. Similarly, prior urological history is needed for patients with neurogenic bladder. In some neurological conditions, there is a higher risk of concomitant upper tract dysfunction, and attention needed to be paid to ensuring an appropriate evaluation has been carried out.

Table 17.2 Contraindications and warnings for botulinum toxin

Active urinary tract infection
Urinary retention
Patient unwilling to perform CIC if necessary (even after counseling and education)
Patient or caretaker unable to perform CIC
Hypersensitivity to botulinum toxin or components in drug
Planned injection will surpass 400 U dose in 3-month interval
Pregnancy
Drug interactions
Active anticoagulation or antiplatelet therapy[a]
Lactation[b]
Myasthenia gravis, Lambert-Eaton syndrome[b]
Immunosuppressed (renal, liver transplant recipients)[b]

[a]Patients should be counseled to hold anticoagulation for 3 days prior to the procedure with consultation with prescribing physician. Dual antiplatelet therapy (aspirin and clopidogrel) should be discussed with the patient's cardiologist. Low dose aspirin (81 mg) may be continued through the time of procedure; however full dose aspirin (325 mg) or clopidogrel should be discontinued at least 5 days prior

[b]Data are limited in guiding treatment in these populations. One must weigh the risk of treatment versus any benefit the patient may gain. Consideration must be given to postpone treatment until the condition is resolved (lactation) or the patient is optimized medically with close follow-up postinjection

There are currently seven FDA-approved indications for onabotulinumtoxinA. Therefore, it is important to determine whether the patient is receiving onabotulinumtoxinA (or other neurotoxin) for any other indication prior to performing intravesical injection. A total of 400 U of onabotulinum toxin is suggested in any one 3-month period, and when possible injections should be performed within 24 hours of each other to minimize the potential risk of antibody formation.

Although botulinum toxin injection is not contraindicated in OAB patients without UUI ("OAB Dry"), one must counsel patients that the highest level of evidence from drug trials included patients with UUI. However, very often patients

may be classified as dry because they have modified behaviors to prevent leaks. Detailed history and close questioning may help elucidate this information. Further, onabotulinumtoxinA, though not FDA approved for PBS/IC, is considered as a fourth-line therapy in the AUA guidelines [67]. This suggests that there is perhaps a role of the therapy on the sensory input from the bladder to the CNS, perhaps more of a factor in some "dry" patients where frequency is driven by sensory urgency. Finally, in some complex cases, the clinician may consider performing urodynamic studies (complex cystometry, pressure flow study, PVR, electromyography) or videourodynamics in OAB patients with refractory symptoms that have failed prior drug therapies and in patients with neurogenic bladder [68].

Some OAB patients experience frustration when primary and secondary therapies are not effective and they are unaware that advanced therapies are available. To prevent this, it is now much more common to present the entire treatment paradigm for OAB to a patient upfront. To do this, many physicians have used clinical care pathways to help the patient navigate to effective therapies. This means that the onabotulinumtoxinA injection as a treatment option may come early in conversations with patients. Either at that point or perhaps more appropriately when the use of onabotulinumtoxinA is being considered, the discussion about the therapy needs to become more intense. Very often this discussion considers other third-line therapies including sacral neuromodulation and posterior tibial nerve stimulation.

When counseling patients about the use of onabotulinumtoxinA for voiding dysfunction, it is important to use terminology that will allow the patient to understand the efficacy and alleviate concerns or anxiety concerning the treatment. Very often we rush beyond the key point of explaining the efficacy of the treatment to discuss uncommon side effect. This is something that needs to be addressed, but the timing in the conversation matters. Additionally, after discussing the success rates and efficacy to be expected, reviewing the duration of drug effect is important. The message of retreatment being a normal part of the therapy should be explained.

The next key message that the patient wants to know about is how the therapy is administered. The patients should be informed that this is a treatment done using a cystoscope, most often with a local anesthetic as an office-based procedure. The "how to" is detailed in the section below.

After explaining the therapy and how it works, the safety of onabotulinumtoxinA injection should be addressed. Urinary tract infection is one of the common adverse events that can occur. Prevention of infection can be reviewed, and treatment of infection can be explained. As an injector, care should be taken to avoid injection when patients are actively infected. Pre-procedure urine analysis is very often sufficient to rule out infections. In patients with a history of recurrent urinary tract infection, indwelling catheter, bacteriuria, or those that are currently performing CIC obtaining a pre-procedure urine culture can allow for culture-specific antibiotics prior to the procedure and avoid last minute cancellation. Many clinicians routinely administer antibiotics prophylaxis periprocedurally. This may be largely due in part to the manufacturer's recommendation to administer periprocedural antibiotics (1–3 days prior to injection, day of injection, and 1–3 days postinjection); however there is no general consensus on periprocedural antibiotic regimens [69, 70]. In our experience, we pretreat based on a recent positive urine culture (see above for specific populations) for at least 3 days prior to injection, treatment day, and 3 days following injection. For uncomplicated patients at low risk of bacteriuria, we shorten the antibiotic course to 1 day of pretreatment, treatment on the day of injection, and postinjection day 1. Ideally, the antibiotic chosen for periprocedural prophylaxis has adequate penetration into the genitourinary system and is cross-referenced with the local antibiogram to cover most anticipated uropathogens. The use of aminoglycoside antibiotics should be avoided as the effect of onabotulinumtoxinA can theoretically be potentiated [69].

The other adverse effect of the procedure is the risk of incomplete bladder emptying. In some cases, this may require transient use of clean intermittent catheterization. Patients should be

counseled about the possibility and must be willing to accept the risk prior to utilizing the therapy. As we gain more experience with onabotulinumtoxinA, we can consider risk stratifying the risk of incomplete bladder emptying and potentially counsel patients accordingly. Elevated PVR, detrusor underactivity, and increasing age may be risk factors for needing CIC after treatment with onabotulinumtoxinA. The authors do not think it is necessary to pre-teach CIC to most patients. In some very select cases where the ability of CIC is questioned and the risk of retention is high, teaching CIC prior to an intervention can be considered. Additionally, clinicians should inform patients that this adverse effect is temporary (on average about 6 weeks in the pivotal trials) and does not affect the overall quality of life improvement.

Off-Label Uses for OnabotulinumtoxinA

There are several "off label" uses for onabotulinumtoxinA that have been used by clinicians in treating various lower urinary tract symptoms and voiding dysfunction. One of the first uses of onabotulinumtoxinA in urological conditions was put forth by Dykstra et al. in the management of detrusor sphincter dyssynergia (DSD) in patients with SCI [21]. Most studies since that time have used onabotulinumtoxinA injections into the external sphincter and have included patients with neurogenic bladder; however, the toxin has been injected into the bladder neck for patients with primary bladder neck obstruction [71, 72]. High-quality evidence is limited for the use of onabotulinumtoxinA for sphincter dyssynergia; however, there is one randomized controlled trial that included 86 patients with DSD and history of MS [73]. Patients in this study were randomized into a group receiving 100 U of onabotulinumtoxinA or placebo (normal saline) injected using a transperineal technique. Both groups were also prescribed an alpha blocker for 4 months. The primary outcome of the study included post void residual (PVR) at 1 month, and secondary outcomes included the International Prostate Symptom Score (IPSS), filling detrusor pressure, and voided volumes. Although no significant improvement was seen in PVR, the patients receiving onabotulinumtoxinA did increase their voided volumes by 54% and decreased their filling detrusor pressure. Despite the apparent improvement noted, one must weigh the benefits highlighted in this study against the potential limitation, and this intervention can place on a neurogenic bladder patient receiving onabotulinumtoxinA for other indications. The procedure is also limited by the dosing frequency every 3 months and discomfort to sensate patients as the urethra is difficult to anesthetize. Furthermore, there are no long-term data on how these improvements translate into better outcomes in terms of quality of life, continence, and upper urinary tract deterioration.

Another application that has been investigated for onabotulinumtoxinA is in the treatment of bothersome lower urinary tract symptoms as a result of Benign Prostatic Hyperplasia (BPH). Several groups have reported on the use of botulinum toxin for BPH with limited success after Maria et al. initially reported improvement in urinary flow rate (Qmax) and AUA symptom score [74, 75]. Despite their enthusiastic findings, subsequent investigators did not find appreciable differences between intraprostatic onabotulinumtoxinA and placebo including two multicenter phase 2 randomized controlled trials performed in the United States and Europe [76, 77]. Overall, both studies found a significant placebo response which compared to responses in the cohorts receiving active treatment. Based on these results, intraprostatic onabotulinumtoxinA injection is not routinely performed.

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a syndrome whereby patients present with an unpleasant sensation perceived to be related to the bladder and associated with lower urinary tract symptoms for more than 6 weeks without a clear etiology to explain symptoms [78]. Several studies have investigated the use of intradetrusor onabotulinumtoxinA injection for the pain and bothersome lower urinary tract symptoms associated with IC/BPS with modest improvements in pain scores, nocturia, and urinary frequency [79–

81]. As described earlier in the chapter, onabotulinumtoxinA works primarily by inhibiting acetylcholine neurotransmission producing a state of chemodenervation. It also exhibits analgesic activity by inhibiting afferent nociceptive signaling thus warranting investigation for its use in patients with IC/BPS [81, 82]. In order to maximize the analgesic effect of onabotulinumtoxinA, certain authors have proposed limiting injections to the trigone of the bladder as this area contains the highest concentration of nociceptive afferent fibers [2, 83, 84]. The published studies available have been limited by small study populations, heterogeneity in patient symptom severity, number and location of injections, utilization of hydrodistention, dose, and follow-up [85]. The largest study population was investigated by Kuo et al. when 67 patients were randomized to receive 100 U or 200 U suburothelial onabotulinumtoxinA injection or hydrodistention alone [86]. All patients were followed up in 2 weeks for hydrodistention, regardless of the intervention they were randomized to. After 3 months, the authors reported statistically significant improvements in cystometric bladder capacity, as well as improved bladder pain as measured by the visual analog scale. The authors reported no additional benefit in using 200 U in comparison to the 100 U dose and found a higher incidence of adverse effects in the patients receiving 200 U injections. Long-term follow-up was reported by Giannantoni et al. where 15 patients underwent submucosal injections in the lateral walls of the bladder and trigone [81]. After 1 year, there was no beneficial effect in pain relief from the intervention, and at 5 months only 26% of patients had pain improved from baseline. The most recent study was a phase 2 double-blind randomized controlled trial performed by Pinto and colleagues where patients were injected with 100 U of onabotulinumtoxinA or normal saline within the trigone (Fig. 17.4) [83, 87]. In contrast to other studies reviewed, the author's protocol did not utilize hydrodistention and the patients had to discontinue other intravesical or oral treatments for IC/BPS (with the exception of nonsteroidal anti-inflammatory drugs, gabapentin, pregabalin, and paracetamol) prior to the study. At week 12, 60% of patients who received onabotulinumtoxinA injections had >50% improvement in pain compared to 22% who received placebo. Patients also demonstrated improvements in quality of life and reduction in micturition frequency. Furthermore, the procedure posed minimal risk with regard to urinary retention as the mean PVR was minimal (5 ± 13 mL). The current guidelines on IC/BPS from the American Urological Association include onabotulinumtoxinA injection as a fourth-line therapy [78]. This therapy should be reserved for patients who have undergone extensive counseling on the risks of urinary retention requiring CIC. This adverse effect may preclude treatment in many patients with IC/BPS as bladder distention, and performing CIC may be particularly painful, thus limiting any efficacy from the treatment. Future advances in the delivery method of onabotulinumtoxinA may serve to benefit patients with IC/BPS. Chuang and colleagues recently published their results of a prospective randomized controlled trial evaluating the use of liposomal formulated onabotulinumtoxinA (lipotocin) in patients with refractory IC/BPS [88]. Unfortunately, the study failed to demonstrate efficacy in this population and improvements from baseline symptoms were largely driven by placebo effect.

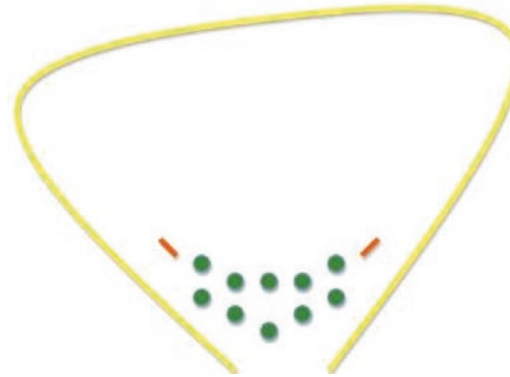

Fig. 17.4 Trigonal injection sites. Green circle marks site of injection. Orange dash indicates location of ureteral orifice. (Reprinted from Pinto et al. [87]. With permission from Elsevier)

Chronic pelvic pain due to pelvic floor muscle dysfunction is a common disorder encountered in many urologic and urogynecologic practices and

has been estimated to affect roughly 15% of adult women [89]. The pathophysiology is not well defined; the condition has been labeled high-tone pelvic floor dysfunction (or levator myalgia) as it is thought to be the effect of hypertonicity of the levator ani complex. Patients may present with myriad of symptoms including bothersome lower urinary tract symptoms, pelvic pain, dyspareunia, and tenesmus. The cornerstone of therapy includes pelvic floor physical therapy; however, other therapies including biofeedback, antidepressants, intravaginal anxiolytics, and trigger point injections have been investigated [90–93]. OnabotulinumtoxinA has been used successfully in relieving pain and function in conditions also characterized by increased resting muscle tone (cervical dystonia, limb spasticity) [94]. Thus, investigators hypothesized botulinum toxin injection into trigger points in the pelvic floor musculature (puborectalis, pubococcygeus for example) would lead to similar symptom control. Abbott and colleagues performed a randomized clinical trial where patients were randomized into cohorts receiving injections of 80 U of onabotulinumtoxinA or placebo (normal saline) and followed for 6 months. The authors found that patients in the onabotulinumtoxinA group had significant improvement in dyspareunia and nonmenstrual pelvic pain measures by visual analog scale. Additionally, there was also a significant reduction in pelvic floor pressure (measured by vaginal manometry) compared to baseline in the onabotulinumtoxinA group. Higher doses of onabotulinumtoxinA in the pelvic floor muscles have been used by Adelowo et al. in a retrospective series including 29 women [95]. Doses administered during the study period varied between 100 and 300 U, and pain improvement was seen in 79% of the study population within 6 weeks. The median time to patient requested retreatment was 4 months, and half of the patients included requested repeat injections. The authors did report adverse effects including urinary retention ($n = 3$) and fecal incontinence ($n = 2$), which occurred in patients receiving 300 U injections and resolved between 12 and 20 weeks postinjection.

Transperineal and transvaginal injections have been described in prior reports [95, 96]. For women, a transvaginal route is preferred as one can elicit trigger points in the levator ani complex and direct injections as dictated by examination. The procedure can be performed under anesthesia however, adequate pain relief can be provided by performing a pudendal nerve block using an Iowa trumpet guide. Injections should pierce the vaginal epithelium at least 1 cm and enter the levator muscles. Prior to injecting, one must withdraw on the syringe in order to prevent intravascular injection. At this point the trigger point injection can begin by directing injections to individual findings on physical exam (Figs. 17.5 and 17.6). After injecting, one may use digital pressure or place a vaginal pack for 5–10 minutes to ensure hemostasis.

Adverse Effects of OnabotulinumtoxinA

Intradetrusor injection of onabotulinumtoxinA for idiopathic OAB and NDO has proven to be a safe and effective treatment with an acceptable risk profile for routine clinical practice. There are important safety considerations clinicians must be aware of to prevent adverse effects as well as a working familiarity with both common and rare side effects. In general, most of the adverse effects that impact patients are localized to the lower urinary tract and easily treated.

As discussed above, the most commonly reported adverse effects with botulinum toxin injection are localized to the lower urinary tract and include UTI and incomplete bladder emptying. The most common adverse effect reported after intradetrusor onabotulinumtoxinA injection is UTI. The rate of UTI is variable in the literature and ranges between 3.6% and 54.5%. Compared to 0–10% incidence of symptomatic UTI following diagnostic cystoscopy, this rate appears to be discordant with the higher rates of UTI after injecting sterile botulinum toxin [97]. This wide range may be due to several factors including a lack of consistency across studies about criteria defining a UTI after injection. For example, in two randomized controlled trials, UTI was based on laboratory data rather than

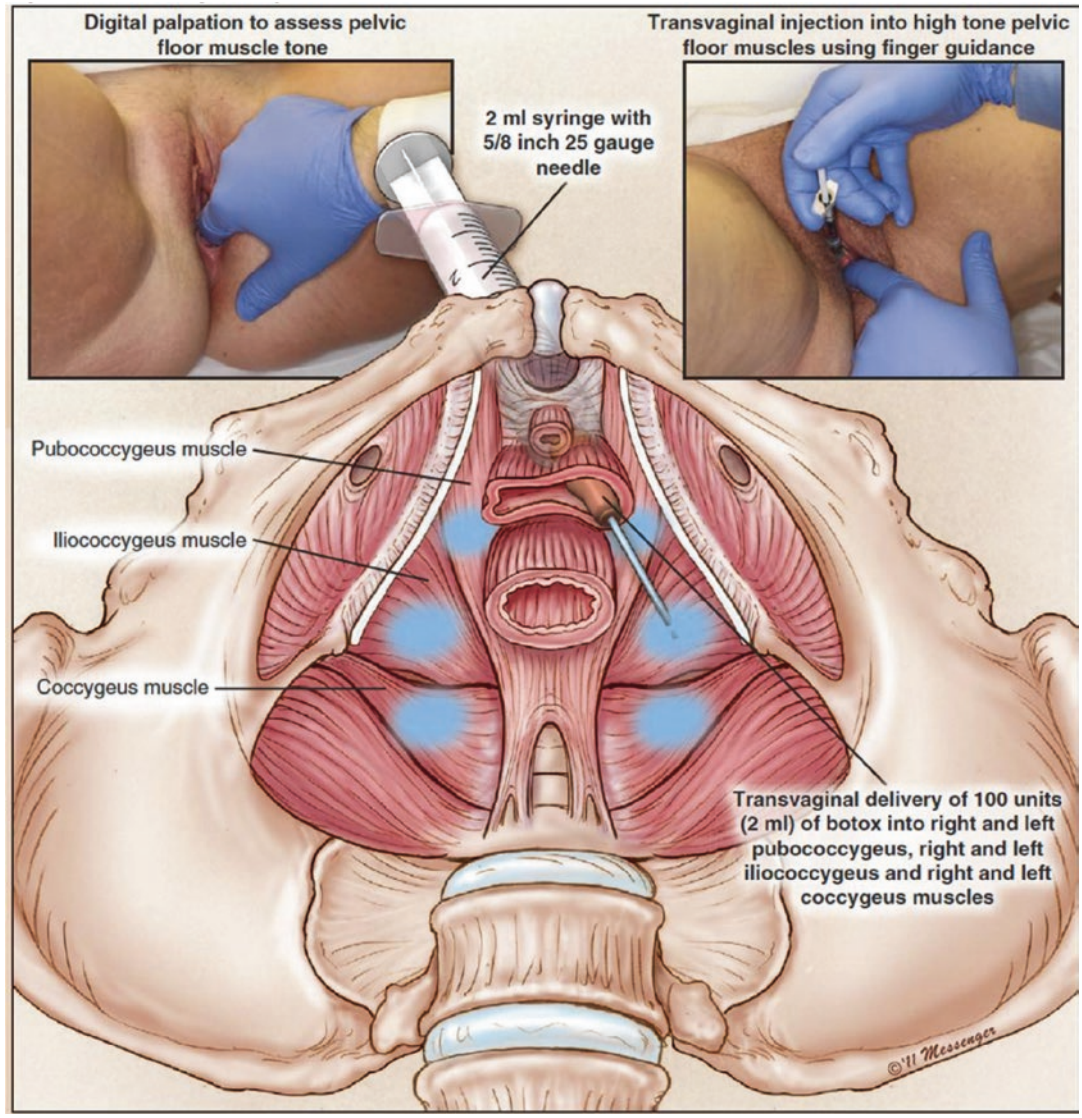

Fig. 17.5 Transvaginal injection of onabotulinumtoxinA into levator ani muscles. (Reprinted from Goldstein et al. [96]. With permission from Elsevier)

relying on patients' symptoms and objective data [26, 58]. This incidence may certainly be influenced by patients with asymptomatic bacteriuria, transient pyuria following cystoscopy, and performing CIC. Additionally, patients receiving this treatment will have bothersome urinary tract symptoms at baseline and persistence or exacerbation of these symptoms can mimic UTI symptoms and thus prompt a workup including urinalysis and urine culture. In one recent systematic review, Stamm et al. evaluated the definition of UTI used by investigators performing cystoscopy with onabotulinumtoxinA injection and compared them with published guideline statements defining UTI [98]. They found that only 54% of the studies that met inclusion criteria reported their UTI criteria. They concluded that future studies must adhere to clearly defined criteria to better understand the incidence of UTI following botulinum toxin injection. In order to prevent this adverse effect, many clinicians administer concurrent antibiotic prophylaxis as

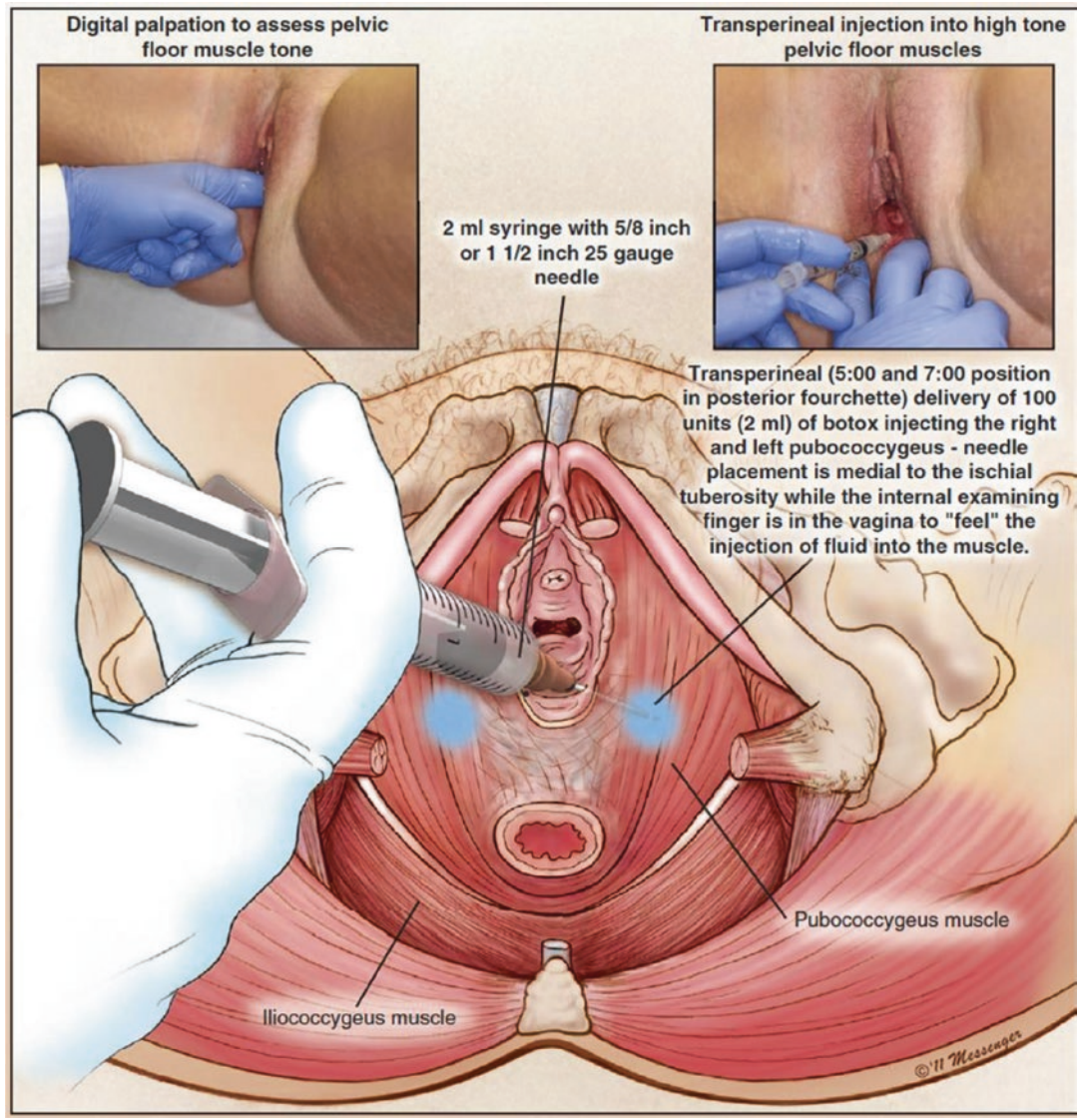

Fig. 17.6 Transperineal onabotulinumtoxinA injection into levator ani muscles. (Reprinted from Goldstein et al. [96]. With permission from Elsevier)

recommended by the AUA clinical guidelines on antibiotic prophylaxis for cystoscopic procedures [99].

Incomplete bladder emptying resulting in elevated post void residual may occur after onabotulinumtoxinA injection; however many patients may remain asymptomatic as a result of this adverse effect. Although this adverse effect can occur at all indicated doses, it seems to occur in a dose-dependent manner. Studies including patients with NDO (specifically MS and SCI) did not have a predetermined volume at which CIC would be initiated, and the decision to begin CIC was largely at clinician's discretion [26]. Approximately half of the patients receiving onabotulinumtoxinA injections that did not perform CIC at the time of recruitment began catheterizing after injection. There was also a significant number of patients (22%) in the placebo arm of the study who began catheterizing, suggesting

that perhaps many patients may have benefited from CIC prior to enrollment. Nevertheless, patients who do not catheterize prior to injection should be counseled appropriately on their risk of incomplete bladder emptying. One must be able to assess the patient's ability to realistically perform CIC and consider teaching CIC prior to injection. In non-neurogenic OAB randomized controlled trials, patient symptoms (difficulty voiding, bladder fullness) were taken into account in addition to the post void residual [58, 59]. When the results of both phase 3 randomized controlled trials were pooled by Sievert et al., CIC was initiated in 5.8% of patients receiving 100 U of onabotulinumtoxinA. Prior to injection, patients who do not perform CIC already should be advised on the potential risk of urinary retention. Discussion can be individualized based on comorbidities and functional status. For example, hand and upper extremity strength, coordination, and tactile sensation should be assessed. Many patients, particularly those with NDO, may also benefit from learning how to catheterize prior to injection. Furthermore, the patient's body habitus and genitourinary tract anatomy should be considered when deciding between CIC and an indwelling catheter should the patient develop urinary retention.

Less common side effects resulting after botulinum toxin injection were also localized to the urinary tract and include hematuria (3–7%), increased incontinence (7%), and bladder pain (1–6%) [26, 58]. However, there is a risk of side effects resulting from distant spread of the toxin to other parts of the body. Symptoms associated with distant side effects can include muscle weakness, difficulty with breathing or respiratory depression, dysphonia, dysphagia, and ptosis. Although rare, these complications have been reported and may occur immediately following the procedure, or in a delayed fashion (weeks) [100, 101]. Furthermore, patients with a history of myasthenia gravis should be counseled on the increased risk of distant effects including muscle weakness. Close follow-up should be performed along with the patient's treating neurologist in order to adjust home medications and monitor for flares in symptoms.

Long-term use from onabotulinumtoxinA injection appears to be safe and effective for both NDO and non-neurogenic OAB [63, 102]. Patients receiving multiple injections in both studies continued to have improvements in UUI and quality of life that were sustained throughout the study periods. Furthermore, the risk of CIC in both studies seemed to diminish with repeat injections, even in those patients who had developed urinary retention with their first treatment. Most importantly, there was no increase in adverse effects with repeat injections, and there were no significant treatment-related side effects outside the urinary tract. Antibody-mediated degradation of botulinum toxin did occur in 2% of NDO patients (all had SCI). No patients receiving the FDA-approved dose (100 U) for onabotulinumtoxinA developed antibodies. Overall, botulinum toxin injection is an efficacious and safe procedure for both neurogenic detrusor overactivity and non-neurogenic OAB.

Injection Technique

Intradetrusor injection with onabotulinumtoxinA can be performed in an office setting or as an ambulatory surgery (sample protocol summarized in Fig. 17.7). In the author's experience, performing botulinum toxin injection in the office is well tolerated in both men and women. Additionally, the procedure is more efficient for both patient and physician as the office setting allows for a controlled workflow without impedance from delays inherent to operating rooms and hospitals (presurgical testing, operating room delays, untrained staff, etc.). In both settings, it is critical to ensure the proper equipment is available and the medication has been properly stored. OnabotulinumtoxinA vials should be stored in a refrigerator (2–8 °C) or freezer (≤ −5 °C). The product in the vial has a fine white grainy appearance and needs to be reconstituted with sterile injectable saline prior to usage. Once it is reconstituted, it can be stored in a refrigerator for 24 hours, and unused medication should be discarded. For OAB, a 100 U dose is recommended, divided into 20 injection sites (0.5 mL per site)

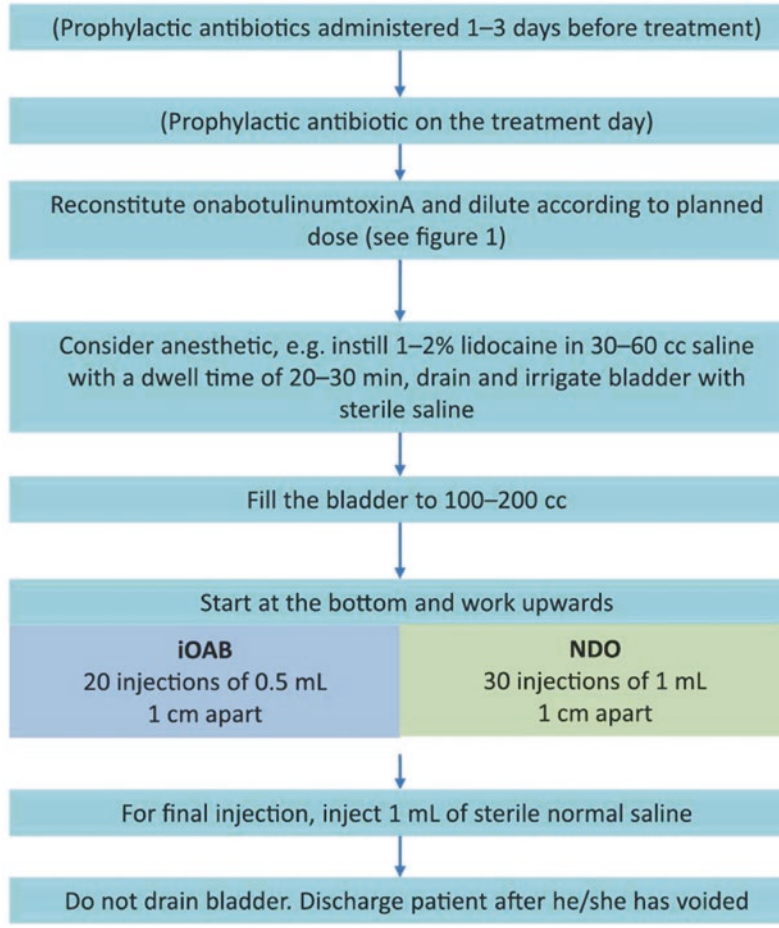

Fig. 17.7 Summarized protocol for onabotulinumtoxinA administration in office setting. (Reprinted from Rovner [105]. With permission from John Wiley & Sons, Inc.)

after reconstituting in 10 mL of injectable normal saline. Proper technique for reconstitution of the drug is demonstrated in (Fig. 17.8). It is critical to avoid shaking or mixing the toxin aggressively as this may disrupt the toxin's disulfide bonds and render it ineffective. For patients with NDO, a 200 U dose is the approved dose; however it is important to note that 100 U injections have been used in NDO patients who are not catheterizing prior to injection therapy (e.g., Parkinson's disease) [45]. The 200 U dose, the reconstituting instructions recommended by Allergan, is paraphrased in the following statements [69]. If using a 200 unit vial, the drug is reconstituted with 6 mL of injectable normal saline and then 2 mL is drawn into three 10 mL syringes. Next, 8 mL of injectable saline is added to each of the 10 mL syringes and mixed gently for a total of 10 mL of reconstituted botulinum toxin. Alternatively, one can use two 100 unit vials and add 6 mL of injectable normal saline into each. Next, 4 mL of reconstituted toxin is drawn into two 10 mL syringes, and the remaining 2 mL from each vial is drawn up into a third syringe. Finally, 6 mL of injectable saline is added to each of the syringes for a total of three 10 mL syringes containing reconstituted botulinum toxin.

In order to perform the procedure in an office setting, the authors prepare the patient to arrive approximately 45 minutes prior to injection with a comfortably full bladder. After the patient voids, he/she is allowed for a urinalysis. After instilling 2% viscous lidocaine, a catheter is used to drain the bladder and instill intravesical local anesthetic. A post void residual can also be recorded at the time the bladder is drained. This

Using the reconstitution needle, draw up the correct amount of saline in the appropriately sized sterile syringe. A 21-gauge, 2-inch needle is recommended for reconstitution. Reconstituted onabotulinumtoxinA should be clear, colourless, and free of particulate matter

Insert the needle straight into the vial, then tilt the vial at a 45° angle and slowly inject the saline into the onabotulinumtoxinA vial. Vacuum is present in the vial, which demonstrates that the sterility of the vial is intact. Do not use the vial if the vacuum does not pull the saline into the vial

Release the vacuum by disconnecting the syringe from the needle and allowing air to flow into the vial. Gently mix onabotulinumtoxinA with the saline by moving vial side to side or rotating the vial

Draw the fluid into the injection syringe by placing the needle into the bottom corner of the vial for full extraction. Do not completely invert the vial

Disconnect the injection syringe from the vial and attach an appropriate needle for injection

Fig. 17.8 Reconstitution of onabotulinumtoxinA. (Reprinted from Rovner [105]. With permission from John Wiley & Sons, Inc.)

is left in situ for approximately 30 minutes. The anesthetic used may vary; however, the author's preference is 30 mL of 1% lidocaine diluted in 50 mL of normal saline. In select patients, sedation or general anesthesia can be used.

Special precautions should be in place for patients with NDO and a history of autonomic dysreflexia or those with high spinal cord injuries (injuries affecting levels at or above T6). These patients may benefit from performing onabotulinumtoxinA injection in a monitored setting. Furthermore, in some cases these patients may benefit from preoperative alpha receptor blockade to prevent unopposed sympathetic stimulation [103].

Injections can be performed through a flexible or a rigid cystoscope using a long injection needle ranging from 21 to 25 gauge. The needle depth can be variable as well as typically ranging between 4 and 8 mm. In the author's practice, a rigid injecting cystoscope is used in female patients. In male patients a flexible scope with a long needle that fits through the working channel is used. When utilizing a flexible cystoscope for botulinum toxin injection, one must be careful to avoid injury to the working channel that can occur from the sharp needle tip. Most needles used with flexible scopes have an outer sheath or a retractable tip to facilitate.

The procedure should begin with an anatomical assessment of the bladder neck, trigone, position of the ureteral orifices, and assessment of the urothelium. Bladder should be partially filled to about 200 mL. Avoiding overdistention reduces the risk of patient discomfort, may prevent perforation, and minimizes inducing an involuntary bladder contraction. Traditionally injections of 0.5 mL of reconstituted medication are per-

formed systematically and under direct vision in 20 separate sites for OAB patients and 1 mL injections in 30 separate locations for NDO. Sites selected should be 1 cm apart and 2 mm deep into the detrusor while avoiding any obvious blood vessels. Through the package insert state 1 cm, most clinicians likely evenly distribute injection throughout the bladder. Some clinicians may opt to inject the afferent laden trigone, while others may elect to follow the pattern used during the registration trials and avoid injecting the trigone.

Proper injection depth can be assessed visually while the drug is being injected and optimized using the proper length needle. For example, if a superficial bleb rises at the injection site, the injection may be too shallow (submucosal), or if there is no change, the drug may be too deep. Ideally, one should visualize a subtle rise in the mucosa underneath the injection site. Minor bleeding may be seen after an injection and may impair visualization; thus we follow an injection template that proceeds from the base of the bladder and work ventrally can be helpful (Fig. 17.9). We begin injecting approximately 1–2 cm cephalad to the right or left ureteral orifice on the posterior wall and continue laterally for the subsequent injections. Once the contralateral side of the bladder is reached (~5 injections), the next column begins a few cm cephalad to the last injection and proceeds laterally. In order to clear the needle of unused toxin and ensure the full dose is administered, the final injection should consist of a small volume of normal saline that matches the volume of the needle used. Bleeding localized to injection sites is typically self-limiting and resolves without intervention. However, if bleeding persists, one may apply direct pressure using the beak of the cystoscope. Alternatively, one can retract the injection needle into the sheath and apply pressure using the blunt tip of the injection sheath. In a minority of patients, monopolar electrocautery using a bugbee electrode is necessary.

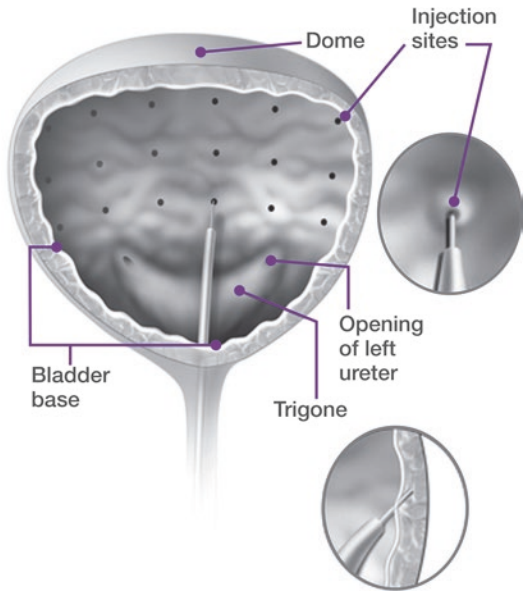

Fig. 17.9 Standard injection template for OAB/NDO. (Courtesy of Allergan, Inc., Irvine, CA, USA)

After the procedure, patients should be monitored and demonstrate the ability to void. For patients performing CIC, they can be instructed to empty their bladder after the procedure. Prophylactic antibiotics are administered to minimize the risk of UTI. Patients are usually given postprocedure expectations and instructions on follow-up. Dysuria and mild hematuria can be expected after most transurethral procedures. They should also be informed that the onabotulinum toxin will not start to show clinical efficacy right way. They should expect about 2 weeks to appreciate an improvement. Furthermore, they should be counseled to contact the clinician if they experience fevers, chills, respiratory symptoms, and generalized muscle weakness. Patients should be scheduled for a follow-up appointment approximately 2 weeks postinjection in order to reevaluate their symptoms, and measure a post void residual and consider a urinalysis if needed. The registration trials for idiopathic OAB CIC were initiated if the PVR was 200 mL or greater, or less than 350 mL with associated symptoms (e.g., difficult voiding or a sensation of bladder fullness), or PVR was 350 mL or greater regardless of symptoms. These cutoffs now can serve as a framework, but more liberal thresholds have also been described [60].

Good practice includes arranging a follow-up a few months after injection to assess symptoms and if needed arrange for a repeat injection.

Closer follow-up may be needed if patients experience suboptimal efficacy or if elevated residuals need to be followed more closely.

For patients with idiopathic OAB who do not respond to 100 U injection, we initially consider reinjection with 100 U of onabotulinumtoxinA 3 months following their initial injection. A higher dose (200 U) may be considered for this patient population, but a higher risk of incomplete bladder emptying must be discussed prior to injection. Furthermore, idiopathic OAB patients with symptoms refractory to chemodenervation may be counseled on other third-line therapies as an adjunct or alternative.

Patients with NDO follow a similar algorithm where reinjection can be performed after 3 months. However, one may consider off-label use of abobotulinumtoxinA as an alternative or consider repeat injection with 300 U of onabotulinumtoxinA [35, 104].

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