Botulinum Toxin Therapy for Voiding Dysfunction and the Female Pelvic Floor

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Background

Onabotulinum toxin A has been utilized therapeutically throughout the past century. Onabotulinum toxin is an acetylcholine release inhibitor and a neuromuscular blocking agent, and for many years was limited to fields outside of urology. Recent research has shed some light on the numerous other applications of onabotulinum toxin A, specifically within Female Pelvic Medicine and Reconstructive Surgery (FPMRS). Herein we discuss the history of onabotulinum toxin A, its use within the field of FPMRS, and potential future indications for use of this unique toxin.

History of Botulinum Toxin

The first descriptions of the actual symptoms of food-borne botulism date back to the nineteenth century, when it was discovered as a toxin found in sausages and pork. Justinius Kerner was the first to describe the effects of the toxin in two monographs in 1820 and 1822 [1]. He later began a series of animal experiments and reportedly self-ingested the toxin in order to better understand how the toxin worked and to determine if there were any potential benefits of the toxin itself.

In 1895, Van Ermengem identified the actual bacteria as *Bacillus botulinum*. Later, this was renamed *Clostridium botulinum*. This bacterium was noted to produce seven distinct antigenic toxins, notably "A, B, C, D, E, F, and G." The first to isolate onabotulinum toxin A in a stable precipitate was Herman Sommer, M.D. at the University of California, in San Francisco, USA in the early twentieth century. It was not until 1946 when Edward Schantz, Ph.D., was able to purify onabotulinum toxin A in crystalline form, allowing researchers to study the drug in greater detail. However, it was not until the 1950s when onabotulinum toxin A was noted by Vernon Brooks, M.D., to block acetylcholine release when injected into a hyperactive muscle. This specific characteristic of onabotulinum toxin A led to its early research in the field of ophthalmology.

Perhaps one of the greatest breakthroughs in medical research with onabotulinum A was with Alan B. Scott, M.D., who initiated several animal studies with the toxin. He discovered that by injecting a small amount of the purified toxin into the hyperactive ocular muscles in monkeys, he was able to realign crossed eyes due to strabismus. At the time, the only alternative to strabismus correction was surgical realignment. After this breakthrough, Dr. Scott collaborated with

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F. Firoozi (ed.), *Female Pelvic Surgery*, DOI 10.1007/978-1-4939-1504-0_17,

others, including Dr. Schantz, to develop onabotulinum toxin A into a therapy for ocular disorders.

In the early twenty-first century, the United States Food and Drug Administration (FDA) approved the drug to treat cosmetic indications such as glabellar lines (frown lines), axillary hyperhidrosis (underarm sweating), and upper limb stiffness due to muscle spasticity. The success of onabotulinum toxin A with these prior indications and the years of research in ocular and neural disease paved the way to study the drug and obtain approval in the field of FPMRS.

Mechanism of Action

Onabotulinum toxin A consists of a light and heavy chain joined by a disulfide bond. The heavy chain allows the binding to the neuron, and the light chain of the toxin inhibits vesicle-mediated neurotransmission at the synaptic cleft by cleaving the SNARE protein SNAP-25 (Fig. 17.1a, b) This prevents docking and fusion of the vesicles with the nerve terminal, thus preventing the release of acetylcholine [2, 3]. The subsequent prevention of acetylcholine release "relaxes" the detrusor muscle, preventing uninhibited bladder contractions. Because bladder instillation (as opposed to injection) of onabotulinum toxin A has also been shown to improve detrusor function, it is theorized that there may be an additional effect at the sensory, afferent level [4]. Onabotulinum toxin A is widely available under the trade names Botox (Allergan Inc, Irvine, CA, USA) and Dysport (Ipsen Ltd, Slough, Berks, UK) (Fig. 17.2).

Use in Neurogenic Detrusor Overactivity

For years, patients with neurogenic bladder were limited to only a few options for treatment of their bladder complaints. Specifically, for the patient with neurogenic detrusor overactivity (NDO), options included watchful waiting, behavioral therapy, anticholinergic therapy, clean intermittent catheterization with anticholinergic therapy, or urinary diversion. The numerous side effects of anticholinergics include dry mouth, dry eyes, constipation, nausea, amongst others, which precludes their use in a great percentage of the population [5]. Because of these side effects, the majority of patients who begin anticholinergics will stop them at some point during therapy [6, 7]. With the success of onabotulinum toxin A injection into skeletal and smooth muscle in other areas, it would seem intuitive that it would provide a benefit in patients with NDO.

Patients with spinal cord injury (SCI) and multiple sclerosis (MS) often have NDO, which can lead to urinary incontinence, and has been shown to produce high storage pressures urodynamically [8]. Schurch and colleagues performed one of the first pilot studies evaluating onabotulinum toxin A for patients with neurogenic bladder due to spinal cord injury [9]. In this prospective, nonrandomized trial, patients who were on intermittent catheterization and had leakage despite anticholinergic therapy were given between 200 and 300 units of onabotulinum toxin A. Six weeks after injection, there was improvement in several urodynamic parameters, including maximum cystometric capacity (increase from 296.3 ± 145.2 mL to 480.5 ± 134.1 mL, $p < 0.016$), and in maximum detrusor voiding pressure (decrease from 65.6 ± 29.2 cmH_2O water to 35 ± 32. 1 cmH_2O, $p < 0.016$). In this study, the effect was noted to last approximately 9 months, when patients required repeat injection. This study also noted an increase in residual volume in treated patients, with residual volume on urodynamic evaluation increasing significantly from a mean of 261.8 ± 241.3 mL to 490.5 ± 204.8 ($p < 0.016$).

The United States Food and Drug Administration approved the drug for use in neurogenic detrusor overactivity in 2011. However, dosing and tolerability of the drug remained unclear. A phase-3 placebo-controlled study evaluated both the 200 and 300 unit dosage in patients with MS or SCI. This study included 416 patients from several centers around the world. The primary endpoint measure was the change in urinary incontinence episodes from baseline to week 6. In both the 200 and 300 unit

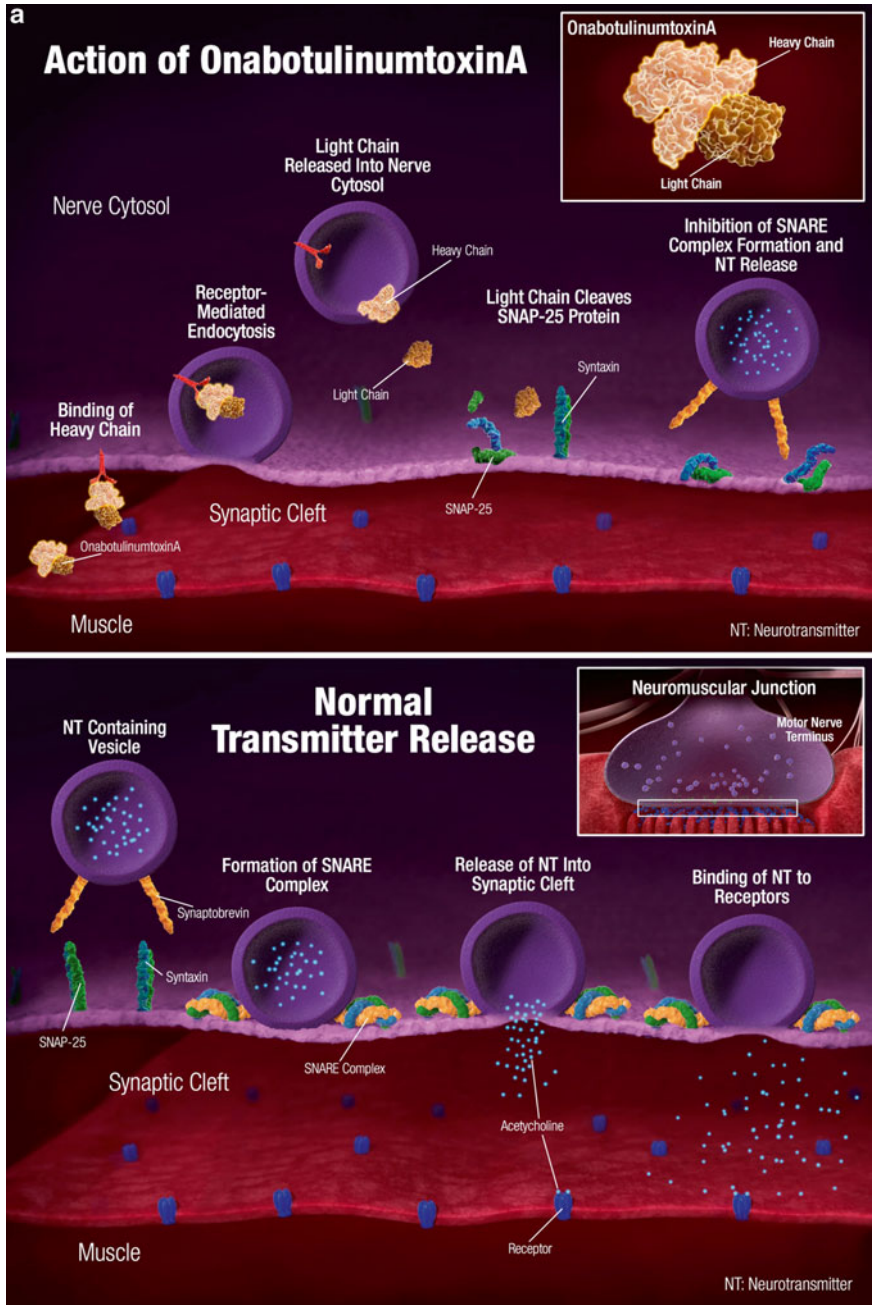

Fig. 17.1 (**a**, **b**) (**a**) Normal cholinergic transmission at the synaptic cleft. (Copyright © Allergan, Inc., Irvine, CA. Used with permission 2013.) (**b**) Onabotulinum toxin A works by inhibiting vesicle-mediated neurotransmission at the synaptic cleft

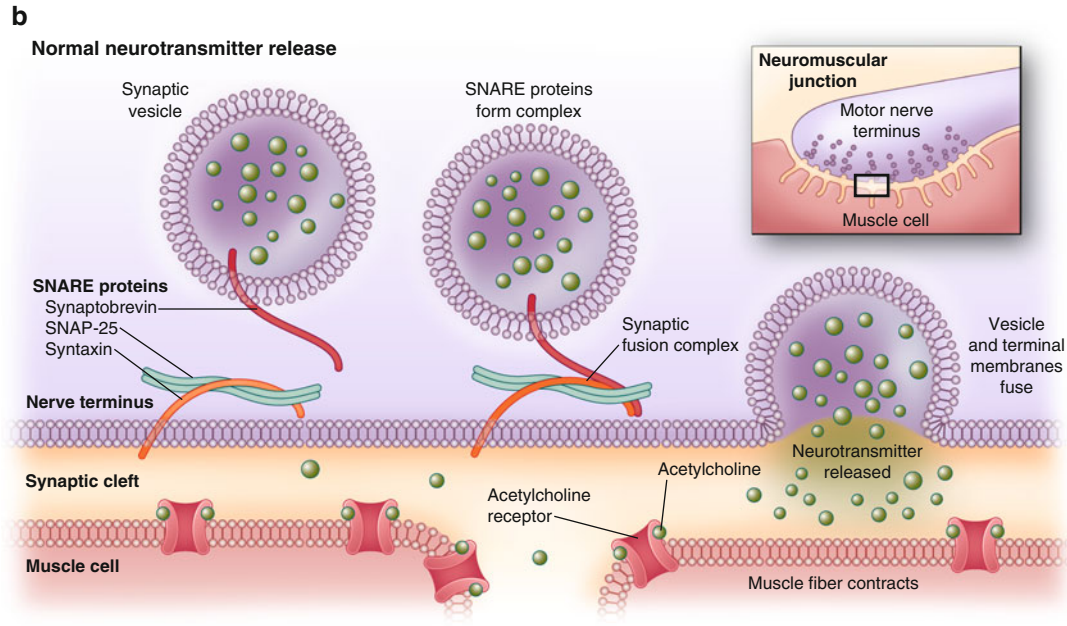

Fig. 17.1 (continued)

Fig. 17.2 Available doses of onabotulinum toxin A which are commonly used in urology applications (Botox, Copyright © Allergan, Inc., Irvine, CA. Used with permission 2013)

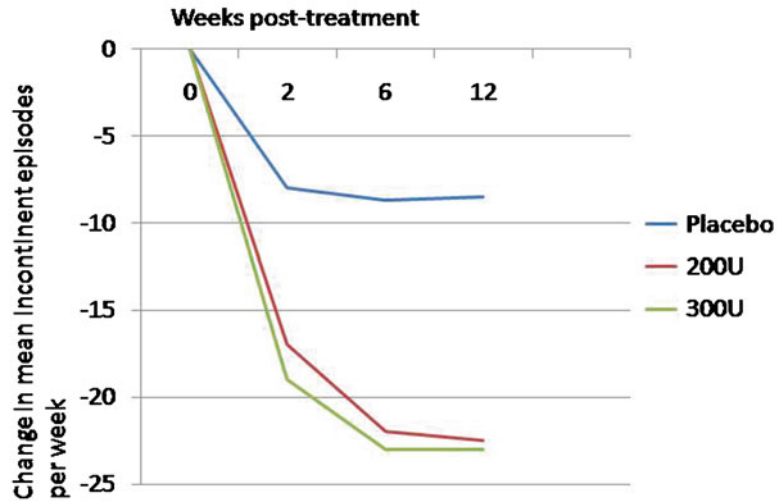

Fig. 17.3 Change from baseline in weekly incontinence episodes with 100 and 200 units of Botox compared to placebo in neurogenic patients (Adapted with permission from Ginsberg D, Gousse A, Keppenne V, Sievert KD, Thompson C, Lam W, Brin MF, Jenkins B, Haag-Molkenteller C. Phase 3 efficacy and tolerability study of onabotulinumtoxinA for urinary incontinence from neurogenic detrusor overactivity. J Urol. 2012 Jun;187(6):2131-9)

treatment arms, mean weekly incontinent episodes decreased to a greater extent than placebo, 21 and 23 vs. 9 episodes per week, respectively (Fig. 17.3). This study had a high rate of postoperative urinary retention requiring intermittent catheterization, with 35 % of patients receiving 200 units, and 42 % of patients receiving 300 units, beginning catheterization. The definition of urinary retention was investigator-dependent, which, in this study, may have led to the somewhat high rates of clean intermittent catheterization in the early data [10].

Use in Idiopathic Overactive Bladder

Approximately 16 % of the adult population has idiopathic overactive bladder (OAB), and approximately 1/3 of these patients have associated urinary incontinence [11, 12]. Patients with OAB are treated initially with behavioral therapy and pharmacologic therapy in the form of anticholinergics or beta 3-agonists. Like NDO, many patients with OAB who begin pharmacologic therapy with anticholinergics are unable to tolerate the side effects of dry mouth, constipation, and dry eyes, and therefore, the majority of patients stop these medicines within months of beginning treatment [13]. Onabotulinum toxin A represents a viable option for these patients, without the untoward side effects typically experienced by anticholinergic therapies.

Brubaker and colleagues compared 200 units of onabotulinum toxin A to placebo in a randomized trial involving female subjects [14]. These women were considered to have OAB with urge incontinence, with a minimum of six incontinent episodes over a 3 day period. Approximately 60 % of women receiving onabotulinum toxin A had a positive effect as evidenced on the Patient Global Impression of Improvement. The median duration of the response in these women was 373 days, compared to placebo, which was 62 days ($p<0.0001$). This study was halted after 43 women were randomized, however, due to increased incidence of urinary tract infection and post-void residual volume in the women receiving onabotulinum toxin A.

Dmochowski published results of a phase 2, multicenter, randomized, double-blind study evaluating multiple dosing of onabotulinum toxin A [15]. Patients with 8 or more urinary urgency

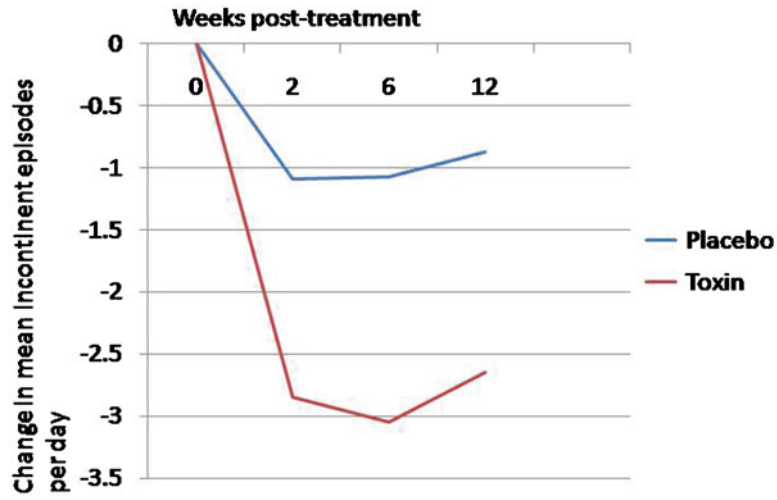

Fig. 17.4 Change from baseline in daily incontinence episodes with 100 units of Botox compared to placebo in patients with overactive bladder (Adapted with permission from Nitti VW, Dmochowski R, Herschorn S, Sand P, Thompson C, Nardo C, Yan X, Haag-Molkenteller C; EMBARK Study Group. OnabotulinumtoxinA for the Treatment of Patients with Overactive Bladder and Urinary Incontinence: Results of a Phase 3, Randomized, Placebo Controlled Trial. J Urol. 2013; 189(6):2186-2193)

incontinence episodes per week and 8 or more micturitions per day were included in the study. Patients received 50, 100, 150, 200, or 300 units of onabotulinum toxin A or placebo. The primary endpoint in this study was urinary incontinent episodes at week 12 after treatment. Efficacy was noted in all groups treated with 100 units or greater of study drug. When dosage response curves were evaluated, it was evident that doses over 150 units did not provide any additional benefit.

Nitti and colleagues reported on the first phase 3 placebo-controlled trial evaluating the 100 unit dose in patients with refractory OAB. Patients with a minimum of three or more urgency incontinent episodes over a 3 day period and with eight or more voids per day were randomized to 100 units of onabotulinum toxin A or placebo. Not surprisingly, onabotulinum toxin A reduced daily incontinent episodes at a greater frequency than placebo (2.65 vs. 0.87 fewer episodes, $p<0.001$) (Fig. 17.4). Total continence rates were 22.9 % in the onabotulinum toxin A group and 6.5 % in the placebo group. Additionally, nocturia, urgency episodes, and volume per void were improved in the study group versus placebo. Therefore, the US FDA approved the dose of 100 units of onabotulinum toxin A in patients with idiopathic OAB.

There is no doubt that reducing urinary frequency and urge urinary incontinent episodes greatly improve quality of life in patients with overactive bladder. Sahai and colleagues demonstrated such a benefit in a randomized, placebo-controlled trial evaluating a 200 unit dose of onabotulinum A [16]. Overall, patients receiving onabotulinum toxin A had a significant improvement in their quality of life when compared with placebo beginning at the 4-week endpoint (median King's Health Questionnaire Incontinence Impact domain score of 33 vs. 0, $p=0.03$). This effect on quality of life improvement appeared to extend to 24 weeks in patients receiving onabotulinum toxin A through the open-label extension study.

There have been few direct comparisons of onabotulinum toxin A to anticholinergic therapy. One study randomized patients with idiopathic urgency urinary incontinence to receive daily solifenacin or trospium (5 mg solifenacin, with escalation to 10 mg, and if necessary, subsequent switch to trospium 60 mg extended release) plus

an intradetrusor injection of saline versus intradetrusor injection of 100 units of onabotulinum toxin A plus oral placebo [17]. Two hundred forty-nine patients were randomized, and patients were evaluated at the 6-month point with voiding diaries and quality of life questionnaires. At 6 months, both groups had significant reduction in daily incontinence episodes (3.4 fewer in the anticholinergic group vs. 3.3 in the onabotulinum toxin A group, $p=0.81$). Patients receiving anticholinergics were more likely to develop dry mouth versus onabotulinum toxin A (46 vs. 31 %, $p=0.02$). Complete resolution of incontinence was noted more commonly in the onabotulinum toxin A group than placebo (27 % vs. 13 %, $p=0.003$). Not surprisingly, patients in the onabotulinum toxin A group had higher rates of urinary tract infection (33 % vs. 13 %, $p<0.001$) and need for catheter use (5 % vs. 0 %, $p=0.01$).

Evaluation, Workup, Procedure, and Post-Procedure

Pre-Procedure Considerations

Typically, patients who have failed conservative therapies such as behavioral modification and anticholinergic or beta agonist therapy or patients who have contraindications to oral anticholinergic therapies are good candidates for injection therapy. Patients should be formally evaluated prior to undergoing an injection of onabotulinum toxin A. Patients presenting with refractory overactive bladder with symptoms of urinary urgency, frequency, with or without urge urinary incontinence should always be attempted on conservative therapy prior to considering procedural therapy for their condition. A formal history to ascertain that patients have failed conservative therapy such as behavioral modification and adequate oral therapy, including dietary history, should be ascertained when evaluating patients for onabotulinum toxin A injection. A 24–48 h voiding diary can often provide insight to voiding symptoms, and daily intake of caffeine and other fluids should be recorded. A basic urologic evaluation consisting of a detailed and proper pelvic exam, residual volume measurement, and urinalysis should be performed. Patients presenting with bacteriuria should be treated appropriately prior to considering injection. Pelvic floor muscle rehabilitation or biofeedback should be attempted as first-line therapy for voiding symptoms. Typically, patients should be tried on oral anticholinergics or beta-agonist therapy prior to being scheduled for onabotulinum toxin A injection.

Once patients have been selected to undergo detrusor injection of onabotulinum toxin A, they must be counseled specifically about the risks of injection, which are discussed elsewhere in this chapter. Because the risk of urinary retention exists, patients should consider learning intermittent catheterization *prior* to injection, should they experience difficulty when the toxin exerts its effect on the detrusor. It is recommended that patients are started on a flouroquinolone antibiotic or trimethoprim-sulfamethoxazole 1–3 days prior to the procedure. Patients should avoid concurrent aminoglycoside administration, as the effects of onabotulinum toxin A have been reported to be potentiated with concomitant aminoglycoside administration in prior studies [18]. Patients should discontinue antiplatelet agents or other anticoagulants prior to injection, if possible.

Surgical Procedure

Intradetrusor injection of onabotulinum toxin A is performed through a cystoscope, in either the office or ambulatory setting. Both rigid and flexible cystoscopes can be used, and there are a variety of needles which are available for injection. There are also rigid cystoscopes designed specifically for needle injection which are small and quite tolerable to the patient with only local anesthesia. Typically, needle gauges range from 21 to 25 gauge. When using needles through a flexible cystoscope, one must be careful not to damage the scope by threading the exposed needle tip through the scope. Therefore, a variety of sheaths and retractable needle tips are available for use during flexible cystoscopy (Fig. 17.5a–d).

Anesthetic choice is surgeon-dependent, and patients should be offered no anesthesia, local

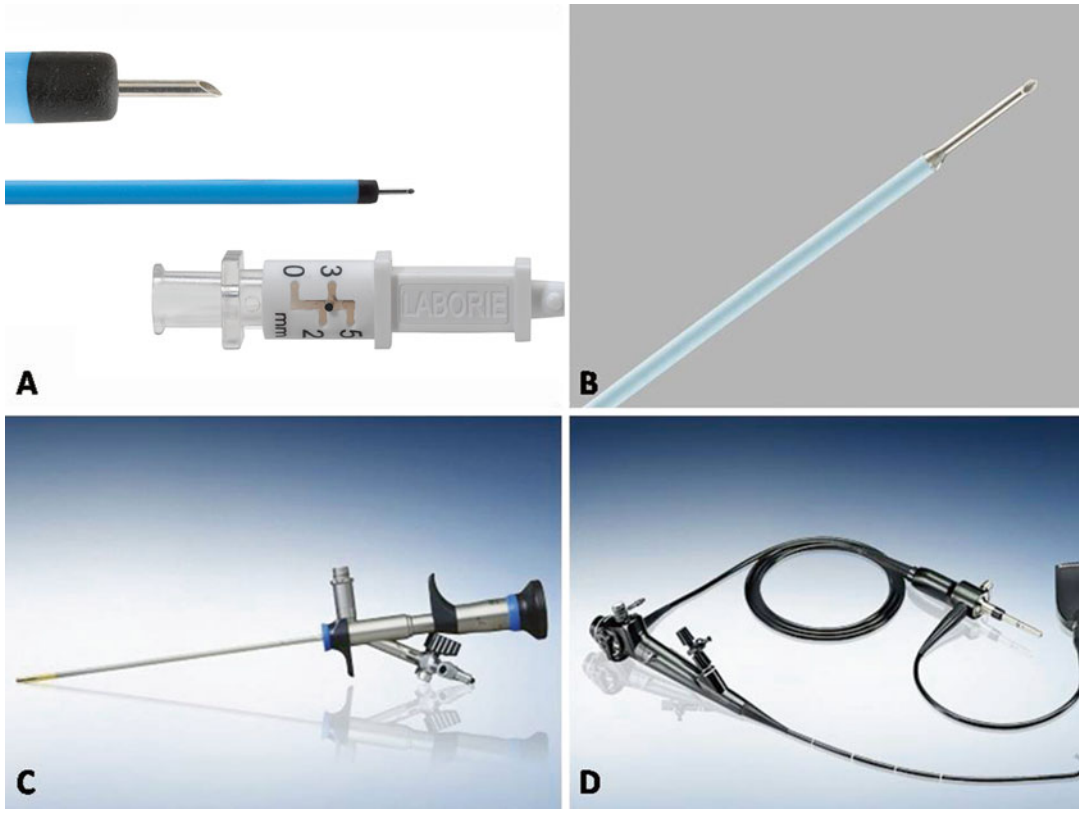

Fig. 17.5 (**a**–**d**) Commonly used instrumentation for injection. (**a**) InjeTAK needle. (**b**) Single-use flexible needle tip. (**c**) Rigid 14 French cystoscope. (**d**) Flexible cystoscope. (**a**: Courtesy of Laborie, Mississauga, Ontario; **b**, **c**, **d**: Courtesy of Olympus America, Inc, Center Valley, PA)

anesthesia, intravenous sedation, or general anesthesia. Special considerations may be made in the patient presenting with NDO and a history of autonomic dysreflexia, as patients may require preoperative blockade to prevent unopposed sympathetic efferent discharge [19]. In the author's experience, most healthy patients with idiopathic OAB tolerate injection in the office setting with simple local anesthetic. Such local anesthetic is in the form of 30–50 mL of 1 % lidocaine, which is instilled via catheter into the bladder. The solution is left for approximately 20 min in order to allow the anesthetic to exert its maximal effect. On the contrary, patients with multiple sclerosis, spinal cord injury with limited mobility may be better served under general anesthesia in order to allow for better positioning during the procedure. The patient is positioned in the lithotomy position, and genitalia should be prepped with sterile solution. The patient is draped, and anesthetic is administered if necessary.

Proper mixing onabotulinum toxin A is of utmost importance, as improper handling prior to the procedure may render the toxin ineffective. Onabotulinum toxin is stored in single-use 100 or 200 unit vials and is commercially available (BOTOX, Allergan Inc., Irvine, CA, USA). The vials themselves contain freeze-dried toxin which is in crystallized form, and is often not visible to the human eye. Botox is reconstituted by instilling 0.9 % normal saline into the vacuum-sealed vials. Total saline reconstituted depends on the total units being administered, in addition to anatomical and clinical considerations. One must remember not to shake the vial, as this can disrupt the delicate disulfide bonds within the

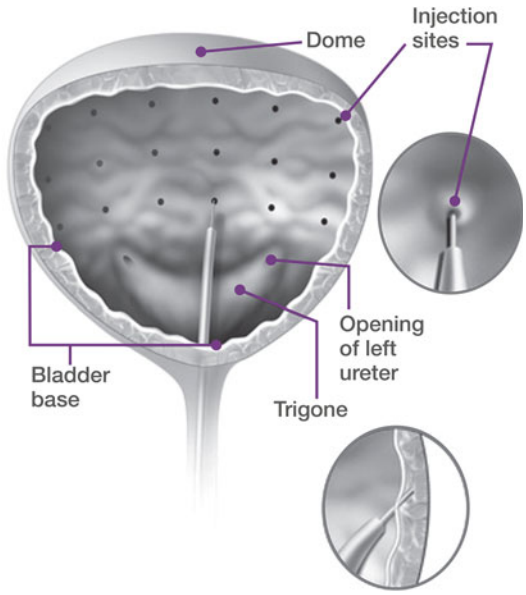

Fig. 17.6 Sites of injection for onabotulinum toxin A into the detrusor. The trigone should be spared, and sites spaced out equally to ensure uniform distribution of the toxin throughout the bladder (Copyright © Allergan, Inc., Irvine, CA. Used with permission 2013)

toxin, rendering it ineffective. Therefore, careful rotation and mixing of the vial is all that is needed for proper reconstitution.

Cystoscopy is briefly performed to map patient anatomy, visualize the trigone and ureteral orifices, and to rule out any papillary mass or lesion. The bladder should be filled with at least 100 mL of sterile water or saline. The reconstituted drug is then injected at a depth of 2 mm, under direct vision at 20–30 equally spaced sites throughout the detrusor, sparing the trigone (Fig. 17.6). The trigone is extremely sensitive especially in patients with only local anesthesia. Furthermore, there exists the theoretical risk of new-onset vesicoureteral reflux if the trigone is injected. Sites should be spaced approximately 1 cm apart. A superficial bleb occurs if the injection is done superficially in the submucosa, whereas no visual change will occur if the drug is injected too deep. A proper injection should result in a subtle visual change and rise of the mucosa under the injection site. The author's technique is to proceed from a left to right (or right to left) manner, beginning each column of injection sites at the bottom, to avoid any minor bleeding from a previous injection site seeping downward and preventing good visualization of the next injection site. For the final injection, 0.5–1 mL of sterile saline is injected in order to inject the remaining toxin, which remains within the needle sheath.

Post-procedure

In patients not already on intermittent catheterization, prior to being discharged after the injection procedure, patients should be able to void spontaneously. It is recommended that patients receive 1–3 days of antibiotics posttreatment in order to minimize the chance of urinary tract infection [Allergan PI]. Patients should be counseled that urinary tract infection is common, and they may have dysuria, or hematuria, as with any cystoscopic procedure.

Because of the mechanism of action of onabotulinum toxin A, the full effect of the procedure may not be noticed until approximately 2 weeks after the procedure. Patients should be scheduled for a visit around that time period in order to evaluate the effect, and a urinalysis, and post-void residual volume should be measured. In general, clean-intermittent catheterization should be initiated only in the setting of symptomatic urinary retention, or if adverse effects of elevated residual volume are deemed dangerous by the investigator, as elevated post-void residual volumes have been shown to be safe and tolerable in several studies in the urologic literature [20, 21]. In the author's opinion, residual volumes of under 350 mL can be treated without the use of intermittent catheterization, provided that patients are asymptomatic.

Adverse Effects of Onabotulinum Toxin A

While the clinical trials evaluating onabotulinum toxin A in both NDO and idiopathic OAB show that onabotulinum toxin A's use is relatively safe, there are important safety considerations which

Table 17.1 Adverse effects of injection of onabotulinum toxin A for neurogenic detrusor overactivity and overactive bladder

Local side effects
Urinary tract infection
Urinary retention
Hematuria
Systemic side effects
Asthenia
Generalized muscle weakness
Diplopia
Ptosis
Dysphagia
Dysphonia
Dysarthria
Urinary incontinence
Respiratory difficulty

practitioners must be aware of. In any instance when onabotulinum toxin A is used, there may be site-specific reactions, in addition to adverse effects due to distant spread of the toxin. Much of the risk lies not only in the site of injection but also in the dosing, as higher doses typically place patients at increased risk for some of the untoward side effects. Therefore, patients should be counseled about these risks specific to their indication (Table 17.1).

Risk of Intradetrusor Injection

Onabotulinum toxin A prevents the release of acetylcholine at the synaptic cleft by cleaving the SNAP protein SNARE-25. Acetylcholine is responsible for detrusor contraction, and by preventing its release, onabotulinum toxin A reduces uninhibited bladder contractions and episodes of urinary incontinence due to detrusor overactivity. However, this same effect leads to incomplete emptying in some patients, due to the decreased contractility of the detrusor after injection. When 300 units was injected in a randomized, placebo-controlled study, the most common adverse event associated with injection was urinary tract infection, with 57 and 55 % of patients developing an infection in both the study drug and placebo group, respectively [22]. In order to minimize this risk, many centers currently administer concurrent antibiotics at the time of injection, per the American Urological Association clinical guidelines on antibiotic prophylaxis with cystoscopic procedures [23].

Elevated post-void residuals are common in all doses, between 100 and 300 units of injection. However, the majority of patients are asymptomatic with respect to these elevations. Early studies on onabotulinum toxin A defined "urinary retention" based on residual volume measurements, and initiated clean intermittent catheterization independent of patient symptoms. In the phase III efficacy and tolerability study evaluating 200 and 300 units of onabotulinum toxin A in patients with neurogenic detrusor overactivity, beginning intermittent catheterization was determined based on the investigator, rather than a predefined residual volume [10]. In patients not already performing intermittent catheterization, particularly those with multiple sclerosis, approximately half (50 %) of patients receiving onabotulinum toxin A began to catheterize. Notably, a significant proportion (22 %) of placebo-injected patients also began to catheterize, which suggests that perhaps many of these patients may have benefitted from learning and performing intermittent catheterization well before being enrolled in the study. Overall, the incidence of urinary retention in NDO appears to be around 21 %.

The incidence of retention appears to be more common with larger doses, and in patients with neurogenic bladder. In the idiopathic OAB trials, investigators were able to lessen the risk of requiring patients begin intermittent catheterization by allowing patient symptoms and investigator judgement to be the determinant of starting intermittent catheterization [15, 20]. In all treatment arms, residual volumes increased significantly when compared to placebo [15]. This effect seemed to peak at week 2, with a gradual decrease between weeks 4 and 12, and the risk of patients having elevations in residual volume was dose dependent [15]. The mean duration of requiring catheterization was highest in the 200 unit group, with a median of 179 days.

By utilizing 100 unit dosing in the OAB population, and by initiating clean intermittent catheterization in patients who are symptomatic due to their retention (despite elevated post-void residual volumes) the true "retention" rate drops to around 6 % [20]. In this patient population, the fear of having to catheterize can be ameliorated by teaching patients how to catheterize before the procedure, as with proper hand function and education, this can be done easily. However, in patients with obesity, poor hand function, or those with challenging anatomy, teaching intermittent catheterization may be challenging, and therefore, indwelling catheters may be required until the effect of the onabotulinum toxin A has worn off.

Other less common side effects related to detrusor injection include hematuria (3–7 %), *increased* incontinence (7 %), and bladder pain (1–6 %) [10, 15]. However, it should be noted that many of these effects are seen in the placebo-treated arms, and therefore, are likely due to the procedure itself rather than the effects of the toxin.

Distant Non-Site Specific Effects

Distant spread of onabotulinum toxin A can occur during use in any site within the body. Death has been reported due to the distant spread of the toxin, however, as of 2013, none have been reported due to the specific toxin-related effects in any of the bladder-related studies [20]. Paralysis of distant muscle groups have been reported in both detrusor and sphincter injections [24, 25]. In a small percentage of patients, generalized muscular weakness can occur (3–7 %), in addition to fatigue (3–6 %), and headache (3–6 %) [10, 18]. These adverse effects can occur within hours to weeks after injection, and therefore patients must be counseled accordingly. In previous studies evaluating patients with NDO and compromised lung function, a small percentage (9–18 %) of patients experienced at least a 15–20 % decrease in forced vital capacity from baseline [18]. These pulmonary effects occurred between 2 and 6 weeks, and appeared to resolve by week 12. Therefore, patients with baseline muscular weakness (particularly the multiple sclerosis and spinal cord injury patient) must be counseled specifically regarding these potential distant effects and monitored closely throughout the posttreatment period.

Potential Long-Term Effects

Injection of onabotulinum toxin A appears to be safe and effective in the treatment of idiopathic OAB and detrusor overactivity due to neurological conditions such as multiple sclerosis and spinal cord injury. Because the effects of the toxin wear off over several months, the majority of patients will require repeat injections within a year of initial injection. There are limited studies evaluating long-term effects after repeated injections. Allergy has been described to onabotulinum toxin A, with the possibility of antibody-mediated degradation of the toxin leading to decreased efficacy over time [26].

Future/Off-Label Indications

Sphincter Injection

In patients with sphincter dyssynergia, onabotulinum toxin A may be injected into either the internal or external sphincter in order to provide relaxation of these muscles to allow for more coordinated voiding. Most studies evaluating sphincter injection have focused on patients with neurogenic bladder due to multiple sclerosis, spinal cord injury, or other neurologic disease with detrusor *external* sphincter dyssynergia. The toxin may also be injected at the bladder neck level, targeting patients with voiding dysfunction due to *internal* sphincter contraction, or primary bladder neck obstruction. Doses of the toxin have ranged from 50 to 200 units and the procedure can be performed in a variety of ways (transurethrally, transperineally, with and without EMG guidance) [27–29]. A recent review of the studies on urethral injection have shown that patients with obstructed flow or sphincter dysynergy can have improvements in several urodynamic parameters, including flow, residual urine

volume, maximal urethral closure pressure, and need for catheterization [28]. Optimal dosing and duration of effect has yet to be determined, although the mean duration of effect in the available studies was 4.6 months.

Pelvic Floor Muscle Dysfunction

High tone pelvic floor muscle dysfunction is characterized by hypertonus of the muscles of the levator ani complex. Pelvic floor spasm may cause chronic pelvic pain, dyspareunia, and voiding and defecatory dysfunction. This condition often exists concomitantly with other pelvic conditions but may present as the most bothersome symptom. Current literature on pelvic floor muscle dysfunction is limited to the use of behavioral therapy, and pelvic floor physical therapy, although a few recent studies have shed some light on the benefit of pharmacological intervention in these patients [30].

In patients with pelvic floor muscle spasm, onabotulinum toxin A injection has been reported to have a potential benefit. While pelvic floor physical therapy remains the mainstay of treatment, injection of onabotulinum toxin A may benefit some refractory patients. In one of the few randomized studies published, Abbott and colleagues injected sixty women with pelvic floor spasm with either 80 units of onabotulinum toxin A or placebo [31]. Patients were followed for 26 weeks, and there was a significant reduction in pain and dyspareunia in the onabotulinum toxin A group versus placebo. Manometry in these patients confirmed that injection of onabotulinum toxin A decreased vaginal resting pressures after injection.

Injections may be done transperineally or transvaginally under anesthesia or in the office setting [32]. In the author's experience, transvaginal injection is the modality of choice, as trigger points can aid the investigator in determining the proper site of injection. An Iowa Trumpet needle guide may be used, along with a 6″ small gauge spinal needle, which pierces the vaginal mucosa and enters the levator muscles. One must withdraw on the syringe in order to ensure no intravascular injection. Doses in previous studies have ranged from 20 to 450 units. In the author's experience, typically 50 units per affected muscle group are injected, with a dilution of 10–30 units per mL. As in other conditions, the optimal dosing and duration of effect is still unknown.

Interstitial Cystitis/Painful Bladder Syndrome

Only a handful of studies have evaluated injection of onabotulinum toxin A in the management of Interstitial Cystitis and Painful Bladder Syndrome. Many of the studies have focused on a dose ranging between 100 and 200 units. Because it is theorized that a defect in the urothelium exists in these patients, several of the studies evaluated submucosal injection, in an attempt to block the release of acetylcholine at the afferent nerve level [33–35]. These studies are limited in patient number with the largest study to date having only 31 patients [34, 36]. There does appear to be some effect, albeit not as impressive as the OAB or NDO trials. In the aforementioned trials, mean daytime urinary frequency improved from 12.5 to 54 %, with improvements in visual analog pain scales ranging from 6 to 79 %. Current recommendations from the American Urological Association Guidelines on the management of Interstitial Cystitis and Painful Bladder Syndrome include detrusor injection of onabotulinum toxin A as a fifth-line therapy for this disease [37]. Of course, patients choosing this therapy must be willing to catheterize or accept indwelling foley catheterization, a side effect which precludes its use in many of these patients.

Vulvodynia

While onabotulinum toxin A may improve pain in women presenting with obvious pelvic floor muscle spasm, its usefulness in treating vulvar disease is less clear. Only one randomized, placebo-controlled clinical trial had evaluated onabotulinum toxin A injection into the vestibule for provoked vulvar vestibulodynia. Interestingly, in both placebo and onabotulinum toxin A

groups, a significant reduction in pain was seen on visual analog scale at 6 months follow-up ($p < 0.001$) [38]. However, no difference was seen between the placebo or onabotulinum toxin A groups ($p = 0.635$). At this time, there appears to be no role in treating vestibulodynia in women.

Conclusions

With the advent of onabotulinum toxin A, the practitioner has an important tool in his or her armamentarium when treating lower urinary tract and pelvic dysfunctions. The early studies showing benefit in neurogenic bladder have paved the way for its use in idiopathic overactive bladder, and likely for its use in several other spastic disorders involving the male and female pelvis. Future studies will be required to better understand ideal dosing, and to identify additional indications for this unique therapy.

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