Botulinum toxin: historical perspective and treatment of neurogenic and idiopathic overactive bladder

**Historical perspective**

“We can be almost certain of being wrong about the future if we are wrong about the past.”

– GK Chesterton.

**Botulinum toxin: from poison to ploughshare**

The term ‘botulism’ comes from the Latin word botulus, meaning ‘sausage’. The first published account of the food-borne illness was traced to sausage in 1820 by German physician Christian Kerner. The symptoms of dry mouth, blurred vision, difficulty swallowing, drooping eyelids, slurred speech, vomiting and, in some, generalized muscle weakness, are all attributable to botulinum toxin (BTX). If the respiratory muscles were affected then the disease was fatal. Kerner isolated the substance from the meat and cadavers of the victims. He then showed the isolated substance to be extremely toxic to animals. Amazingly, over 150 years before his time, he suggested this substance might be used in the future as a therapeutic agent against involuntary movements in patients with neurologic disease [1].

While this is the origin of the word botulism, this food-borne illness has likely accompanied mankind throughout antiquity. There are older case reports describing patients with dilated pupils and flaccid paralysis. These incidents were attributed to belladonna intoxication. Belladonna plant extract was commonly used to dilate women’s pupils, a trait at that time considered beautiful. It is now known that atropine, the active ingredient in belladonna, only affects parasympathetic muscarinic receptors and would not cause skeletal muscle paralysis. These older texts probably describe patients with botulism [2].

The anaerobic bacterium that produces BTX, now called *Clostridium botulinum*, was first isolated by Emile van Ermengem, who worked in a laboratory with Robert Koch. This occurred in 1895, after an outbreak that originated from ham at a funeral in Belgium. Outbreaks of botulism continued throughout the world in the early 1900s, till improvements in canning processes were developed. In the following years, seven different antigenically distinct strains of BTX, labeled A to G, were discovered, based on their differing ability to activate antibodies [2].

The next major scientific discoveries regarding BTX came not from medical research, but from the military during the world wars. Biological warfare fears led military scientists on both sides to study and purify BTX. The toxin was developed by the USA and separately by the British military. Both were serotype A (BTX-A). Long after the war, these two strands of BTX-A would eventually be brand-named Botox® and Dysport®, respectively. These brand names are not interchangeable, as the doses are different due to differing potencies. For this reason, the brand names will be used where indicated in this review.

Overactive bladder (OAB) afflicts nearly 17% of the population, causing frequent urgent dashes to the bathroom, sometimes with leakage along the way. This causes difficulties with employment, as well as social and even sexual relationships. The costs of consultations, medications, physiotherapy, surgery, pads, undergarments, cleaners for carpet or furniture, catheters and the treatment of skin and bladder infections has been estimated to be US$32 billion. OAB is not a fatal disease like botulism, but those who suffer from OAB can feel as if their lives have been paralyzed by their bladders. Botulinum toxin can paralyze the bladder in turn, and has emerged as a possible treatment of this epidemic. How botulism was discovered is a testament to early scientist–physicians. The story is fascinating, and how different militaries purified the toxin, a possible weapon of mass destruction, is equally frightening. The medical potential of the toxin was predicted by the very physician who discovered botulism, and the 175 clinical trials currently listed at clinicaltrials.gov attest to the conversion of this substance from killer to healer.

**KEYWORDS:** Botox®  botulinum  neurogenic bladder  overactive bladder  urinary incontinence

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review, rather than the usual convention of using the generic name [2]. It is generally accepted that one unit of Botox is equivalent to 3–4 units of Dysport [1].

In 1968, an army officer working with the toxin named Edward Schantz was approached by an ophthalmologist, Dr Alan Scott, and together they injected BTX to correct strabismus in monkeys [1]. Partly delayed due to a biological warfare treaty, the first publication of human injection was not until 1980, in patients with strabismus [3]. Over the following decades, BTX would be injected therapeutically for several disorders characterized by increased striated muscle contractility. It would receive US FDA approval for treatment of strabismus, blepharospasm and hemifacial spasm in 1989, and in 2000 for cervical dystonia. However, Botox would not become a household name until it received FDA approval in 2002 for the cosmetic treatment of facial wrinkles, namely glabellar lines.

Dykstra and colleagues first described the use of BTX in urologic disease, treating detrusor–sphincter dysynergia in spinal cord injury (SCI) patients in 1988 [4]. A total of 10 years later, Stohrer and Schurch were the first to inject the smooth muscle of the bladder with BTX in the treatment of what is now called neurogenic overactive bladder (OAB) [5]. Since then, BTX has been used for idiopathic detrusor overactivity (IDO), overactive bladder (OAB), interstitial cystitis and benign prostatic hyperplasia. Some have even used it with direct visual internal urethrotomy to treat urethral stricture disease, and even prostate cancer. As the off-label uses of BTX continue to grow, this one-time poison was purified for war, but has become a potent agent of healing.

**Botulinum toxin & acetylcholine: not the whole story**

The inhibition of acetyl choline (ACH) transmission from the presynaptic neuron by BTX was shown as early as 1949 [6]. Since this is the cause of muscle paralysis and death in patients with botulism, it is not surprising it is the most well-known and studied biochemical pathway of BTX. BTX-A is made up of a light chain and a heavy chain linked by a disulfide bond. The heavy chain is responsible for binding the neuron’s plasma membrane and penetrating it. Subsequently, the light chain enters the cytoplasm without the heavy chain, and ultimately prevents the release of ACH. ACH is stored in the cytosol in membrane-bound vesicles to prevent breakdown. These vesicles fuse with the nerve plasma membrane when the nerve fires, and release ACH into the synapse. Prior to release, the vesicles are docked along the neuron plasma membrane near the synapse by specific proteins called SNARE proteins. This docking allows vesicles to fuse to the plasma membrane quickly in response to depolarization. Different BTX toxins interfere with different docking proteins to inhibit ACH release by preventing vesicle fusion, and this in turn prevents subsequent muscle contraction [7] (see Figure 1).

These vesicles, which fuse with the plasma membrane, are normally recycled by the cell, and there is evidence to suggest that BTX-A uses this recycling system to gain entry into the cell. One protein that the heavy chain of BTX binds is called SV2, and is actually a synaptic vesicle protein. SV2 gets incorporated into the plasma membrane when the vesicle fuses. As a result, SV2 is present in a greater quantity on the plasma membrane of neurons that are actively fusing vesicles to the plasma membrane [8]. Once BTX-A binds SV2 and the vesicle is recycled by the neuron and brought back into the cell, the BTX is said to be internalized. However, the light chain must still gain access from the recycled vesicle to the cytosol in order to perform its function. To do this, BTX-A undergoes a pH-dependent conformational change that causes a cleavage of the light and heavy chains. The heavy chain then helps to form a pore within the vesicle membrane and allows the light chain to exit the vesicle into the cytoplasm. The light chain then inactivates docking proteins either on the vesicles (BTX-B, D, F and G) or on the nerve plasma membrane (BTX-A and E). BTX-A specifically cleaves the SNAP-25 protein, called SNAP-25 [7] (see Figure 1).

The inhibition of cholinergic transmission by BTX at the motor end plate of skeletal muscle adequately explains the symptoms of botulism and the early therapeutic uses for BTX. In urology, this same mechanism acting on ACH release at cholinergic parasympathetic detrusor synapses likely accounts for the effectiveness with which Botox prevents so-called uninhibited bladder contractions seen on urodynamics. These contractions define the urodynamic diagnosis of detrusor overactivity (DO). However, ACH should be released during the voiding phase, which does not easily explain the effective treatment of urgency with BTX. Urgency has been defined as ‘the sudden compelling desire to void that is difficult to defer’, and has become the hallmark symptom for OAB [9]. BTX has been effective at reducing urgency. If BTX acts only
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on efferent cholinergic nerve activity that should be present primarily during micturition, how urgency is reduced is yet to be fully determined.

Theoretically, anticholinergics treat the nervous system outflow or efferent activity at the same synapses. However, anticholinergics block ACH at postsynaptic muscarinic receptors rather than preventing release of ACH like BTX. BTX has been effective in many patients in whom anticholinergics fail. Whether BTX is more effective because of more efficient blockage of neurotransmission at these efferent synapses or because of additional mechanisms is still not definitively known. The increased efficacy of BTX may be solely related to higher potency than anticholinergics on efferent cholinergic activity. However, it seems logical that some additional mechanism beyond partial bladder paralysis may be present. In addition, genetic deletion of SNAP 25 does not result in a complete block of ACH release, suggesting that even the BTX-mediated inhibition of ACH release might occur via other mechanisms [10]. In fact, the very classification scheme of afferent and efferent is debatable given the propensity of neurons to express characteristics of the other class. With this caveat, this generalization will allow easier presentation of the effects of

**Figure 1. BTX-A mechanism of action on cholinergic transmission.** First BTX-A binds the presynaptic membrane by interacting with a membrane-bound protein, termed SV2. This protein is present on vesicles containing ACH, and when these vesicles bind to the plasma membrane the ACH is released and SV2 is then present on the cell plasma membrane. Therefore, more active neurons that are releasing ACH will have more SV2 present on the plasma membrane, and BTX-A selectively gains access to the intracellular environment of more active neurons. Next, the BTX-A is brought inside the plasma membrane when the vesicle is recycled. Still BTX-A must gain access to the cytosol from inside this membrane-bound vesicle. Here, the heavy chain forms a pore and allows the light chain to break off and enter the cytosol after separation. Following this, the BTX-A light chain cleaves a specific SNARE protein responsible for docking ACH-filled vesicles near the plasma membrane. This specific SNARE protein has been labeled SNAP-25. Other non-medical strains of BTX, designated letters other than ‘A’, inactivate other SNARE proteins. Without ACH-containing vesicles docked along the plasma membrane at the synapse, ACH cannot be released during depolarization, and therefore the nerve transmission is effectively inhibited.

ACH: Acetylcholine; BTX: Botulinum toxin.
BTX. However, the high degree of integration of afferent and efferent systems should be kept in mind. Moreover, there appears to be a growing complexity to bladder physiology involving the interplay between the detrusor smooth muscle, the urothelium and interstitial cells or myofibroblasts, as well as these neurons. This ingrained layered system has been termed the myovesical plexus.

Anticholinergics require only a basic understanding of the physiology of voiding, but perhaps overemphasize the efferent component of the CNS and perpetuate the idea that bladder filling is a purely passive process. The most distinctive and redeeming quality of BTX may be the ability to treat both the abnormal sensory activity associated with urgency and defining OAB, as well as the bladder contractions of DO. By treating the problem on both ends, the nonselectivity of BTX may be its greatest asset. The increasing use of BTX may also force a greater appreciation for the complex physiology of the bladder wall and the process of accommodation during filling. As BTX is shown to affect an increasing number of neurons or neurotransmitters, understanding its biochemical mechanism of action becomes tantamount to deciphering the growing information on the neurophysiology of micturition and the pathophysiology of DO.

While a complete explanation of micturition physiology and the effects of BTX on this is beyond the scope of this review, briefly, BTX has been shown to act on multiple layers of this myovesical plexus. BTX inhibits the release of substance P (SP), calcitonin gene-related peptide (CGRP) and glutamate from rat sensory ganglia if given access to the intracellular environment [10]. BTX has been shown to inhibit CGRP release from isolated rat bladders. Intravesical BTX inhibited CGRP release in rat inflammatory bladder models. In a single study of OAB human bladders, BTX induced a progressive decrease and eventual normalization of the vanilloid receptor TRPV1 and the ATP-gated purinergic receptor P2X3 [11].

**Clinical results**

Understanding the clinical results of detrusor injection of BTX is also difficult, because multiple small studies have been performed and, within these studies, patient populations vary greatly. Given the multiple possible mechanisms of action, it is not surprising that BTX has been used in the broad disparate group of patients who could be diagnosed with the ‘catch-most’ diagnosis of OAB. This includes patients with DO, both neurogenic detrusor overactivity (NDO) or IDO, wet and dry patients, and even in OAB with urodynamics showing a lack of DO. Many studies lump these patients together, while others focus on various subgroups (see Box 1). This table does not even take into account that incontinence can be classified as pure urge or mixed incontinence. Perhaps most amiss, few studies specifically selected men or women who have very different bladder outlets and voiding dynamics. These populations may also contain unknown numbers of patients who meet standard definitions of chronic pelvic pain syndrome or interstitial cystitis. These two groups have also been separately studied using BTX. Almost all studies did require a previous failed trial of anticholinergics. Most studies involved patients undergoing a first injection with BTX-A. Differing dosages of Botox and Dysport were often used, not to mention the fact that differing dilutional volumes were used for the different dosages, and that the number of injection sites also often varied between studies.

Further complicating the outcome analysis, some studies used clinical parameters such as daytime frequency, nocturia, urge incontinence episodes and number of pads used. Some used differing validated questionnaires, while others did not. Many studies used various urodynamic parameters such as maximal cystometric capacity, detrusor compliance, first desire to void, volume at strong desire to void or urgency volume, detrusor compliance, and volume with DO – the reflex volume.

The various distinctive categories within OAB have allowed many studies to be published on the effects of BTX detrusor injection in slightly differing patient groups. Most studies have been open-label and small. A few controlled trials have been performed, some of which were randomized. The results of these studies show that despite heterogeneous patient populations and outcome parameters, BTX was consistently effective and beneficial based on both measurable clinical and urodynamic outcomes, as well as various validated quality-of-life questionnaires.

<table>
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<th>Box 1. 18 possible patient populations.</th>
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<tr>
<td>* OAB</td>
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<td>* NOAB</td>
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<td>* NDO</td>
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<td>* IDO</td>
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DO: Detrusor overactivity; IDO: Idiopathic detrusor overactivity; IOAB: Idiopathic overactive bladder; NDO: Neurogenic detrusor overactivity; OAB: Overactive bladder; NOAB: Neurogenic overactive bladder.
With a few notable exceptions, the efficacy of BTX-A injection in treating the symptoms of OAB has been established, and no group listed in Box 1 appears refractory to this treatment.

A European consensus report for the treatment of lower urinary tract disorders has been recently published online. Like previous reviews, efficacy outcomes of adult DO and OAB are divided into neurogenic and non-neurogenic. This report provides an evidence-based review of the current applications of BTX in urology. This report identified 1018 patients with NDO treated with Botox in two randomized, controlled trials, one randomized active comparator trial and 22 open-label studies. Other included studies used Dysport, the British-derived BTX-A that differs in potency. Most patients in the review had NDO as a result of SCI or multiple sclerosis. Most were treated with 30 injection sites of a total of 300 U of Botox reconstituted in normal saline to a dilution of 10 U/ml. A systematic analysis of different doses has not been performed, but the general range for Botox is 100–300 U, although one study of 400 U has been performed [12,13]. The range of injection sites was 15–40. The tendency toward using the 300 U versus the lower 100 U dose is not surprising in this patient group, given that approximately 84% were already performing clean intermittent catheterization (CIC). However, not all studies specified this vital pretreatment statistic [14]. Despite disparate study designs and patient populations, consistent benefit was measured in nearly all parameters. The consolidated results are listed in Table 1. The ranges in the table list values from the various studies, not from individual patients. The mean changes are weighted averages [12].

Despite this overall success, one interesting caveat is a lack of efficacy found in a small subset of patients with NDO secondary to a cerebrovascular accident. In this group of 12 patients isolated from one open-label study, only one achieved complete continence. The impact of functional incontinence or dementia was not assessed [14]. This low value was excluded from the range listed in Table 1. Interestingly, these cerebrovascular accident patients still showed improved results in urodynamic parameters. Other than this caveat, there were consistently positive results in nearly all measured efficacy parameters. There are currently ongoing Phase III clinical trials using Botox for the treatment of NOAB, which can be found on the clinicaltrials.gov website [101–103].

These consistently positive outcomes led to BTX-A injection in non-neurogenic OAB/IDO patients. In this group, the European consensus report similarly identified 589 non-neurogenic OAB patients with or without DO treated with BTX-A in 25 single first injection studies. Some studies allowed a second injection in patients who failed to show improvement. Overall the consensus panel identified one small randomized, controlled trial, three randomized trials comparing different Botox doses or different injection techniques and 21 open-label studies [12]. There are notably absent studies from the European consensus panel, including a multicenter randomized, control trial from the USA [9]. In this group the possible side effect of urinary retention requiring catheterization becomes more important, as most patients in these studies were not performing CIC.

As in the neurogenic studies, these studies lack homogeneity in design and outcome measures, but still demonstrated consistent improvements in clinical and urodynamic parameters. The dose range was again 100–300 IU of Botox, but the most common dose in this population more at risk for new urinary retention was lower, at 200 IU. The only randomized, controlled trial in the consensus report contained patients

<table>
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<th>Table 1. BTX-A efficacy in adult neurogenic overactive bladder.</th>
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<td><strong>Outcome</strong></td>
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<tr>
<td>Number of incontinence episodes</td>
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<tr>
<td>Maximum cystometric capacity</td>
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<tr>
<td>Maximum detrusor pressure</td>
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<tr>
<td>Percentage of patients having periods of complete continence between catheterizations</td>
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<td>QoL questionnaire change versus baseline</td>
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Data comes from two placebo-controlled trials, one active comparator-controlled trial and 22 open-label studies and was compiled by a European consensus panel convened in January 2008 [12].

QoL: Quality of life; SCI: Spinal cord injury.
with IDO with or without incontinence. The 16 patients in the treatment arm had significant improvements in frequency, urge incontinence, maximal cystometric bladder capacity and quality-of-life (QoL) scores compared with 18 controls [16]. Table 2 shows the cumulative data of the consensus report, again with the range indicating outcomes in various included studies rather than individual patients [12].

These consistent improvements in patient parameters establish the efficacy of BTX in this population as well. Tables 1 & 2 show compiled data from a few randomized, controlled trials and multiple open-labeled trials, and display the consistent efficacy of BTX-A in neurogenic and non-neurogenic populations. This leads to good overall confidence regarding the efficacy in treating the varied patients with OAB. Compliant patients already performing CIC make the best candidates for BTX detrusor injection, as the known drug effect of urinary retention requiring CIC is the main adverse event of concern.

While this European consensus report wonderfully compiles efficacy data summarized in Tables 1 & 2, it justifiably falls short of tabulating a convincing de novo CIC rate after BTX injection in the catheter-naïve patient. This is because data from individual trials used such disparate post-injection indicators for requiring de novo CIC. Some used numerical post-void residual (PVR) cut-offs, while others used clinical parameters such as symptomatic UTI, new hydronephrosis, renal failure or urinary retention. Now that the efficacy has been established, efforts should focus on defining a logical consensus for de novo CIC indications. A post-injection rate can then be calculated, and patients appropriately counseled. However, this may be tantamount to deciphering the significance of PVR and bladder urine stasis. The maximal voided volume may better capture the retained detrusor activity than the PVR. This value should also be recorded in all studies. Men and women should be separated, if not in study design, then in outcome analysis, due to their differences in outlet resistance and subsequent required voiding pressures, as well as their differing tolerances of CIC.

In an effort to summarize the numerous patient subsets in Box 1, reviews have usually divided the data into a group of NDO and a second group of non-neurogenic OAB (NNOAB) or IDO, just as is done here in Tables 1 & 2. While this distinction between neurogenic and non-neurogenic allows results from certain studies to be compared, the benefit of distinguishing neurogenic and non-neurogenic outcomes is questionable and primarily historic. NDO was treated first with BTX because of the classic known mechanism of action on the efferent nervous system outflow. However, more importantly, most of these neurogenic patients already required CIC prior to injection. This makes these patients at no risk for the known drug effect of urinary retention, perhaps the most significant ‘side effect’ of intradetrusor BTX.

For this reason, the number of patients in a study who do not already require catheterization is more important than the presence or absence of neurologic disease. All neurogenic patients in the randomized, controlled trial and the active comparator trial using Botox in neurogenic DO were on a regimen of CIC prior to treatment [17,18]. Unfortunately some studies do not include this information. A recent systematic review of BTX in NOAB/NDO demonstrated that in 13 of 18 articles, the pretreatment bladder emptying modality was specified. Of these, CIC was being carried out in 84% of patients [14]. For this reason, results

<table>
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<th>Outcome</th>
<th>Mean</th>
<th>Range (by study)</th>
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<tr>
<td>Percentage of patients experiencing periods of complete continence between voids</td>
<td>58%</td>
<td>32–86%</td>
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<tr>
<td>Percent reduction in incontinent episodes</td>
<td>65% decrease</td>
<td>35–87% decrease</td>
</tr>
<tr>
<td>Maximum cystometric capacity</td>
<td>65% increase</td>
<td>11–303% increase</td>
</tr>
<tr>
<td>Percent frequency change</td>
<td>35.5% decrease</td>
<td>12–55% increase</td>
</tr>
<tr>
<td>Percent urgency change</td>
<td>50% decrease</td>
<td>22–88% decrease</td>
</tr>
<tr>
<td>QoL questionnaire change versus baseline</td>
<td>48% increase</td>
<td>23–93% increase</td>
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Data comes from two small, randomized, controlled trials, three randomized trials using different doses or injection techniques and 23 open-label studies, which was compiled by a European consensus panel convened in January 2008 [12]. QoL: Quality of life.
from studies in neurogenic patients are usually extrapolated to patients already on a CIC regimen. Surprisingly, there is much less information on patients with chronic indwelling catheters. One small case series has been published involving only three patients with end-stage multiple sclerosis and urethral urinary leakage despite indwelling suprapubic catheters. BTX injection achieved continence in all three [19]. An open-label study of 200 patients with NDO and urge urinary incontinence specifically noted 12 patients with indwelling catheters. Unfortunately these patient outcomes were not listed separately [20]. Given the large number of patients with so-called ‘catheter bypassing’ urinary incontinence, it seems logical that further studies in these patients should be performed.

The percentage of patients on CIC with IDO is much less. This population is inherently at higher risk for requiring de novo CIC. Analysis of this negative potential treatment outcome is difficult due to under-reporting of the percentage of patients already requiring CIC preoperatively in some studies. However, even more problematic are the varying definitions of urinary retention and differing indications for CIC. This may account for the variable rates of de novo CIC after injection, which range from 0 to 45% [12].

While the need for de novo CIC does appear to be dose-related, no ideal dose has been identified. In addition to the ideal total dose, the number of injection sites, the dose and dilution per each injection site and the ideal location of these injections has not been elucidated. This ideal dose and injection technique would theoretically treat the urgency, frequency and urinary incontinence of OAB patients, and yet would still allow enough detrusor contraction to occur so that the bladder consistently empties effectively. It would therefore eliminate the ‘overactivity’, but still allow the normal detrusor activity.

Whether or not such a dose and technique can be found depends on the chosen indicators for CIC. Some studies have used numerical PVR cut-offs ranging from 100 to 400 ml [21]. There is wisdom in the old medical adage that says ‘don’t treat the numbers.’ The use of BTX in non-catheter-dependent populations is likely to both challenge long-held ideas regarding PVR cut-offs and further clarify the significance of residual bladder urine and voided volume. One study specifically designed to assess the need for CIC after repeated BTX injections randomized 44 idiopathic overactive bladder (IOAB) patients to 100 or 150 U of Botox, which was injected via flexible cystoscopic injection sparing the trigone and dome. Of these 44 patients, four who received 150 U and one who received 100 U required de novo CIC. Systematic PVR measurements were recorded postoperatively, but arbitrary cut-offs to initiate CIC were not instituted, as had been done in other studies. Instead, this group’s indication for CIC included only symptomatic patients with pain or discomfort, inability to urinate, urinary tract infection or hydronephrosis on ultrasound [22]. The overall risk of CIC will likely need to be low if most patients with IOAB are going to accept Botox injection treatment. Further studies are required to see how BTX use may interfere with the early signs and symptoms of outcomes like infection and retention, to see if patients present with more advanced forms of these potential complications.

In addition to dose, injection technique may play a role in the development of urinary retention. Initial techniques described used rigid cystoscopy [5], but flexible cystoscopic injection using ultrafine needles has been described [23] and tolerance [24] and efficacy of the procedure has been shown [25]. These developments are unlikely to have an effect on efficacy, but instead affect the healthcare costs associated with this treatment and may push towards repeated in-office injections. Urologists should be aware that patients with SCI may be at risk for autonomic dysreflexia when considering BTX office injection. However, interestingly, one study showed the disappearance of autonomic dysreflexia during urodynamics after BTX injection in four patients who had previously had this problem, and this improvement persisted for 18 months [18].

While initial techniques spared the trigone, how trigone or bladder base injection relates to the need for de novo CIC, if at all, is not known. One small study of ten adult women who underwent BTX treatment with trigone injection for OAB showed no de novo development of vesico-ureteral reflux on videourodynamics. One patient who had bilateral low-grade reflux preoperatively showed no worsening on VUD [26]. Temporary de novo vesicoureteral reflux has been reported in pediatric literature [27].

In addition to questions regarding injection location, the proper number of injections is not known. Various dilutions of the 100–300 U of Botox using different numbers of injection sites have been described. Most studies that established the efficacy in NDO used 300 U of Botox, diluted to 10 U/ml using approximately 1 ml per injection in 30 sites [14]. There has been a published report comparing the benefit of submucosal rather than intradetosuor injection
of toxin, with the hope of decreasing diffusion and potentially optimizing the concentration near the site of action [28]. Data did not prove that suburothelial injection was superior, but it did show this method to be effective. This same study also compared injection in just the bladder base to injection in the bladder body. While bladder capacity was increased to a greater extent with bladder body injection, bladder base injection did treat urgency, suggesting that sensory urgency may partly be mediated through sensory fibers in the trigonal area. The recent European consensus panel recommended injecting the trigone based on this and basic science evidence that BTX affects the sensory nerves located there [12].

The optimum dose, site and number and even depth of injections have yet to be fully determined. Studies using patients already on CIC should attempt to determine the relationship between higher doses and safety and longer efficacy. New studies in patients without catheter dependence should seek the lowest effective dose so as to best avoid de novo CIC. In addition, injection technique studies should focus on patients primarily complaining of urgency rather than leakage to see if injection dose and location can be modified so as to maximize afferent BTX treatment and retain detrusor contractility. Already, there are ongoing Phase II clinical trials comparing different doses, as well as bladder instillation rather than injection of BTX [104–106]. Men and women should be analyzed separately.

The neurogenic or CIC-dependent OAB population, in whom treatment results have been proven the most, is the proper population in which to ensure safety and dosage parameters with Phase III studies. Care should be taken in large-scale studies to assess the frequency of rare side effects like paralysis of distant muscle groups that have been anecdotally reported [29,30]. While these events are rare, all physicians should be aware of their possibility. Physicians using BTX in off-label indications should familiarize themselves with an FDA update on BTX safety that can be found in the ‘Early Communication about an Ongoing Safety Review of BOTOX’ [107]. This document from the FDA specifically states that there is an ongoing review of BTX safety, and mentions potential systemic effects of Botox injections: ‘The most serious cases had outcomes that included hospitalization and death, and occurred mostly in children treated for cerebral palsy-associated limb spasticity.’ Higher doses of Botox are used for conditions such as skeletal muscle spasticity than in intradetrusor injections. The following is an excerpt from this FDA safety review.

“Until such time that FDA has completed its review, healthcare professionals who use medicinal botulinum toxins should:

- Understand that potency determinations expressed in ‘Units’ or ‘U’ are different among the botulinum toxin products; clinical doses expressed in units are not comparable from one botulinum product to the next;
- Be alert to the potential for systemic effects following administration of botulinum toxins such as: dysphagia, dysphonia, weakness, dyspnea or respiratory distress;
- Understand that these effects have been reported as early as one day and as late as several weeks after treatment;
- Provide patients and caregivers with the information they need to be able to identify the signs and symptoms of systemic effects after receiving an injection of a botulinum toxin;
- ‘Tell patients they should receive immediate medical attention if they have worsening or unexpected difficulty swallowing or talking, trouble breathing or muscle weakness.’

Despite the four anecdotal reports of systemic weakness from intradetrusor injections [29,30] and the above warning from the FDA, these authors recommend the continued usage of BTX for OAB, and feel that counseling patients about these rare side effects is sufficient enough action at this time. In addition, a recent systematic review and meta-analysis of safety data taken specifically from randomized, controlled trials of any of the various medical uses of BTX failed to identify even one such severe adverse event in any trial [31].

**Future perspective**

In patients already undergoing CIC there is no question regarding the efficacy of BTX in treating the symptoms of OAB, improving urodynamics and raising scores on QoL questionnaires. In this population, small randomized, controlled trials have proven the role of BTX as an increasingly effective second-line agent after the all too common failure of anticholinergics. Future studies within this group should be designed to establish a relationship between dosage and duration of effect. Safety at higher doses should be studied carefully; as there is some evidence that rare adverse side effects like distal muscle paralysis are dose dependent. Large-scale studies should try to assess the frequency of these rare side effects. Such adverse events have been anecdotally reported even in
the treatment of urologic disease [29,30]. Still, this neurogenic population, in whom treatment results have been proven convincingly, is the proper population in which to ensure safety and dosage parameters. Some of these studies are underway [101–103]. In addition, the dosage and duration of response demands specific attention because it will be this expensive treatment’s durability that will ultimately determine the sustainability of its use.

Patients with indwelling catheters and so-called bypass urinary incontinence are a population with only anecdotal evidence for effectiveness at present [22,23]. This population will no doubt also prove to be vastly responsive to BTX therapy. They are at no risk for the known BTX drug effect of urinary retention. Slings and bladder neck closures may become less common for patients with suprapubic catheters and urethral incontinence. Instead, BTX will soon be used to either prevent or reverse the bladder changes seen with long-term catheterization.

Improvements in urodynamic parameters will make BTX the mainstay of treatment for patients with poorly compliant bladders who fail anticholinergics [32]. This will help to avoid invasive procedures like bladder augmentation and ileal loop diversion. Some bladders may have enough scarring or fibrosis to be resistant to BTX injection. These bladders may require repeat injections to see if compliance can be returned.

While the clinical indication for BTX in patients already catheter-dependent is clear, the question of de novo urinary retention in the more common OAB patient remains unanswered. Can the bladder be treated in such a way that a patient’s symptoms adequately diminish, and yet enough detrusor contractility is spared to allow effective bladder emptying? Can patients strain or crede to void effectively? What is the indication for CIC? What numerical value of PVR predicts other adverse measurable events such as infection, discomfort or new hydroureteronephrosis? Will the bladder treated with BTX prevent early warning sensations of infection or retention, causing patients to present with more advanced forms of these complications? Perhaps the PVR should be listed as a percentage of the voided volume or bladder capacity? Perhaps maximal voided volume or even post-injection urodynamics determined parameters will predict who will require CIC?

The possibility of de novo CIC and the significance of an elevation of PVR is clearly the most critical aspect of BTX usage in the huge population of OAB patients. Certainly, patients’ PVRs are increased, but the significance of this is uncertain. If the symptoms of an elevated PVR are less than the OAB symptoms, is it safe to convert a bladder that empties too frequently to a bladder that empties incompletely? It appears from the current studies that many patients do prefer a relaxed bladder with elevated PVR to their previous symptoms. They do not appear on urodynamics to be developing high pressures that would risk damaging the upper urinary tract. Their bladders are more compliant, despite their elevated PVRs. While the chance of de novo CIC will likely decide if BTX is widely used in this population, the indication for CIC is unclear.

Defining a PVR cut-off that indicates looming retention is difficult. This definition will be critical in determining the de novo CIC rate, and may be arbitrary. PVR rules in men regarding urinary retention have been set and broken. Temporary elevation of residuals in a chemically denervated bladder has unknown significance. Having a low PVR cutoff for instituting CIC eliminates the long-term risks of elevated residuals and places the responsibility on patients to maintain bladder drainage. However, the other result of this is that many patients may avoid this treatment due to this outcome.

Another option is treating patients symptomatically. Patients could be counseled that if they get bothersome recurrent infections or symptoms of their higher PVR, or urinary retention, then they will require CIC. Also, if urodynamics exhibited pathologic tolerance to high bladder pressures or even high pressures at typical daily volumes, then they should institute CIC. Certainly the PVR should be followed and patients should be made aware of their residual. Classic conservative measures like timed voiding can be instituted. The voided volumes may in fact be more important as they may predict preserved detrusor contractility. Overall, this system of treating symptoms seems prudent.

However, residual urine has been blamed for everything from lower urinary tract symptoms to increased risk of bladder cancer in bladder diverticuli, making it difficult to tolerate high residuals without any reservation. Current ranges across different studies of the risk of requiring de novo CIC are too broad to adequately counsel patients. It is impossible to even compare different studies due to differing CIC indications. Should patients be made to perform CIC prior to BTX injection, or simply agree to the presently unclear risk of this outcome? Certainly BTX is indicated in those
Executive summary

- Botulinum toxin (BTX) intradetrusor injection is clearly efficacious in treating the symptoms of urgency, frequency, urge incontinence and poor bladder compliance, resulting in an overall improvement in quality of life for patients who are already undergoing clean intermittent catheterization (CIC).
- BTX is clearly effective in treating these same symptoms in patients who are not undergoing CIC, but the risk of requiring CIC after injection remains unknown. This possible requirement may significantly impact a patient's assessment of their quality of life postoperatively, despite adequate treatment of their initial complaints.
- BTX intradetrusor injection long-term safety data continue to grow. Rare serious side effects of distal muscle weakness after injection have been reported. All patients should be made aware of these possibilities and counseled to watch for signs and symptoms that would require further medical assistance.
- BTX will be used in the future to treat patients with indwelling urethral or suprapubic catheters and so-called catheter bypass incontinence.

Bibliography

**Papers of special note have been highlighted as:**
- of interest
- of considerable interest


Another excellent review, comparable with [12], with the best effort thus far to determine the rate of de novo clean intermittent catheterization (CIC) using compiled data of discordant study designs.


**Websites**

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